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SYMBOLS OF SIGNIFICANCE

DILANTIN SODIUM.

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Analysis of 402 Cases of Carcinoma of the Breast*

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IN spite of the tremendous advance in breast surgery that took place with the introduction of the radical mastectomy by Halsted and Willy Meyer in 1889, and the refinements in radiation therapy during the past quarter century, we are still faced with the appalling fact that the mortality from carcinoma of the breast is increasing, that it was responsible for 10 per cent of the cancer deaths in the United States registration area in 1935. Spackman and Hynes[13] estimate that 2 per cent of all females die of mammary cancer. These figures certainly drive home the fact that what is needed at present is a new fundamental approach—that there is no satisfactory solution to the problem until we have solved the riddle of cancer.

Mammary cancer is a disease that is localized early, that is soon widely disseminated both by the lymphatics and the blood stream, and whose tumor emboli may lie dormant for many years before becoming activated. What appears to be a primary operable case is frequently not so. Ewing[4] has stated that a tumor under 2.5 cm. in diameter is rarely disseminated—but we seldom see them that small.

The great controversy today is over the management of primary operable carcinoma that has already involved the axillary nodes. There is fairly uniform agreement that the 70-80 per cent five-year salvage obtained in small movable lesions localized to the breast[8]—the anatomical stage I†—with immediate radical surgery is not significantly improved by the addition of irradiation. In anatomical stage II management, there is no such uniform agreement—neither first in defining an operable case with axillary involvement, nor, second, in the management of it. The scope of the surgeon's knife is gradually being narrowed. Factors which must be considered include the histologic characteristics of the tumor, the quadrant of the breast affected,[2] involvement of the skin, and degree of involvement of the axillary nodes. Warren and Tompkins[15] found that their five-year arrents with surgery varied from 68 per cent to 19 per cent depending on whether only one or more than 50 per cent of axillary nodes were involved.

Bartlett found only 4 per cent of five-year arrests when the tumor was in the inner hemisphere, as contrasted with 32 per cent in the outer hemisphere. Harrington[7] operates on any case "in which there is a reasonable chance for cure." Haagensen[5] has neatly outlined what he believes are the criteria of operability—with which we are in full agreement. (Chart I.)

CHART 1.

HAAGENSEN-STOUT CRITERIA OF OPERABILITY—CONTRA-INDICATIONS[5]

1. When the carcinoma is one which developed during pregnancy or lactation.
2. When extensive edema of the skin over the breast is present.
3. When satellite nodules are present in the skin over the breast.
4. When intercostal or parasternal tumor nodules are present.
5. When there is edema of the arm.
6. When proved supraclavicular metastases are present.
7. When the carcinoma is the inflammatory type.
8. When distant metastases are demonstrated.
9. When any two, or more, of the following signs of locally advanced carcinoma are present:
   (A) Ulceration of the skin.
   (B) Edema of the skin of limited extent (less than one-third of the skin over the breast involved).
   (C) Fixation of the tumor to the chest wall.
   (D) Axillary lymph nodes measuring 2.5 cm., or more, in transverse diameter, and proved to contain metastases by biopsy.
   (E) Fixation of axillary lymph nodes to the skin or the deep structures of the axilla, and proved to contain metastases by biopsy.

* From the Tumor Clinic, Stanford University School of Medicine, San Francisco.

† *Anatomical Staging.*

I. Small movable lesion localized to breast.

II. Movable lesion in breast with axillary metastatic nodes that are not fixed.

III. Fixed local lesion. Fixed axillary nodes. Extensive skin involvement. Spread of cancer beyond axillary nodes. Inflammatory carcinoma.

It is hard to decide what policy to adopt in regard to irradiation (preoperative and postoperative). Many statistical studies on this point are available. The criteria used are not uniform, and there is almost as much difference in percentage of success among different observers for each method of treatment as there is between different methods of tratment. (Table I.)

TABLE 1.—*Recent 5-Year Survival Statistics (Arrests)*

	No. Cases	Stage II	All Cases
A. Radical Surgery Only.			
Harrington[7] (1946)	5,407	30.4%	47.6%
Haagensen[6] (1942)	640	21.0%	36.1%
Adair[1] (1943)	172	47.3%	63.0%
Portmann[11] (1943)	?	50.0%	?
B. Pre-Operative Irradiation and Radical Surgery.			
Soiland[12] (1942)	?	47.0%	47.0%
Pfahler[9] (1938)	97	53.5%	44.5%
Adair[1] (1943)	582	35.3%	49.0%
C. Radical Surgery and Postoperative Irradiation.			
Pohle[10] (1942)	42	28.0%	?
Pfahler[9] (1938)	310	47.0%	47.5%
Evans, Leuceutia[3] (1939)	302	?	50.0%
Portmann[11] (1943)	?	65.0%	?
Strenstrom[14] (1945)	254	?	51.0%
Adair[1] (1943)	277	41.8%	54.0%

POLICY AT STANFORD UNIVERSITY SCHOOL OF MEDICINE

Stage I. The present policy at Stanford is immediate operation in all stage I and stage II carcinomas (except for constitutional contra-indications). If no cancer is found in the axillary nodes, nothing further is done unless recurrences appear.

Stage II. If cancer is found in the axillary nodes, postoperative irradiation is given, usually as soon as the sutures are removed.**

The entire hemithorax, including axilla, supraclavicular region, and mediastinum are irradiated to skin erythema—usually between 2,400 and 3,000 r as measured on the skin. The axilla and supraclavicular regions are cross-fired from behind to a total of 3,000 to 3,500 r. This course is not repeated. Further therapy is only in case of recurrences. In all women still menstruating, prophylactic roentgen castration is advised.

From about 1935 to 1940 we were giving all Stage II cases a trial of irradiation. If the tumor responded we carried the dose on to tolerance (usually between 3,500 r and 4,500 r in air to the tumor site) and rested with that, taking the sensitivity as a measure of anaplasia and presumptive operative incurability. But if after some 2,000 r the tumor had not responded, x-ray was stopped and radical operation done immediately. There were only 22 cases so handled.

Stage III. In Stage III, the treatment is highly individual, and almost always primarily irradiation. Simple or radical mastectomy is occasionally done later when all possible x-ray has been given and the controlled local lesion shows signs of regrowth. The few primary radical mastectomies done have convinced us of the folly of attempting this procedure.

** Based on the results of this survey routine postoperative roentgen therapy has been discontinued.

Distant metastases and recurrent cases: X-ray therapy is first directed to control pain, and the local lesion is frequently a secondary consideration. Palliative irradiation has accomplished so much in so many patients that we find ourselves enthusiastic for more treatment in these cases however many times recurrent and widespread the metastases (especially skeletal). The only exception is in the case of hepatic metastases, for which not much relief can be hoped. In the younger group, roentgen castration has occasionally helped considerably.

ANALYSIS OF CASES

During the period of 1926-1945, 402 patients with carcinoma of the breast were seen in the clinics of the Stanford University Hospital. Clinically these were classified according to Steinthal.*

The final classification, and that used in the tables, is anatomical, Stage II consisting of operable cases with axillary involvement. Stage III includes cases of inflammatory carcinoma, of marked skin involvement and/or local attachment, of fixed axillary nodes, and of supraclavicular extension. Stage IV consists of cases with distant metastases. Recurrent cases are those sent in for therapy after recurrence, the primary surgery having been done elsewhere.

Table II gives the distribution of our cases. Thirteen, or 4.3 per cent of our own cases, have been lost while living and well, the greatest number, seven, in Stage I. These have been omitted in computing Stanford survival statistics, though the 16 patients dying of intercurrent disease without evidence of cancer have been included in the gross Stanford survival statistics. Eighty-three cases of our total have been seen since 1941, and

TABLE 2.—*Anatomical Stages, 402 Cases of Breast Carcinoma Seen in the Stanford University Hospital Clinics, 1926-1945*

Stage	Number of Cases	Per Cent
I	90	22.4%
II	109	27.3%
III	83	20.6%
IV	27	6.7%
Recurrent	93	23.0%
Total	402	100 %
Paget's Disease	5	
Males	7	
Females	397	
Cases lost to follow-up	13	3.3% Total Cases 4.3% S.U.H.*
Total cases, 1926-41	319	
Total cases, 1941-45	83	
Total primary S.U.H. cases, 1926-41	229	
S.U.H. cases lost, 1926-41	11	
Died, intercurrent disease, 1926-41	16	

* Stanford University Hospital.

* We have not strictly adhered to the original Steinthal classification, in Stage I, as regards size and rate of growth. Some of our tumors have been larger and have grown more rapidly than the original Steinthal classification would admit.

319 cases up to 1941. Of these, 218 primary cases have been followed five years or more, and form the basis of our present report. Table III gives the age distribution, breast, and the quadrant distribution, when known. Table IV gives the duration of the tumor previous to therapy, where known. In our recurrent group, this data is frequently missing. As would be expected a larger

TABLE 3.—*Age Incidence*

Age	Per Cent
1-20	00.0%
21-40	14.6%
41-60	53.5%
61-	32.2%

BREAST INVOLVED

Breast	No. of Cases
Right	202
Left	188
Bilateral	12

BREAST QUADRANT (S.U.H. Cases)

Quadrant	No. of Cases
Upper outer	158
Lower outer	31
Upper inner	59
Lower inner	33
Unknown	28

TABLE 4.—*Duration of Tumor Before Treatment*

Time	Stage I	Stage II	Stage III	Recurrent
0- 6 mo.	54—61%	56—52%	34—35%	25
6-12 mo.	12	23	15	7
1-2 yrs.	9	18	15	7
2-3 yrs.	3	4	11	1
3-5 yrs.	9	2	11	2
5 yrs.	2	4	12	4

6.7% of patients had a tumor over five years before therapy.

percentage of Stage I cases were seen within six months than those in the other groups. Also 12 per cent of Stage I tumors were so slowly growing that the patient went three years or over before becoming alarmed enough to seek medical advice. Harrington[7] found in his total of over 5,000 cases that 95 per cent of all Broders grade I and 64 per cent of all grade II were without axillary metastases when first seen, but these two groups comprise only 20 per cent of all cases.

Table V gives the distribution of patients in terms of treatment received.

TABLE 5

Type of Treatment	Total S.U.H. Cases	Stage I	Stage II	Stage III, IV
X-ray only	89	6	4	79
Radical only	128	72	46	10
Preoperative x-ray—				
Short	5	0	5	0
Heavy	18	3	7	8
Postoperative x-ray	57	4	45	8
Simple mastectomy	3	2	1	0
Simple mastectomy with heavy preoperative x-ray	3	0	0	3
Simple mastectomy with postoperative x-ray	5	3	1	1
Totals	308	90	109	109

Total radical mastectomies, S.U.H.—202.

ANALYSIS OF RADICAL MASTECTOMIES

During the period of 1926-1941, 202 patients with carcinoma of the breast were treated on the Stanford Surgical Service by radical mastectomy. The operations were performed by different operators, the majority by the surgical residents.

The radical operation consisted in the removal of the entire breast, the skin overlying the breast, a much wider zone of the deep fascia, both pectoral muscles and the gland-bearing fat and areolar tissue from the axilla, all being removed together in one piece. In most instances the clavicular portion of the pectoralis major was preserved. In outlining the skin incision no consideration was given to the possibility of primary closure. If the skin could not be approximated without too much tension then the edges were sutured to the chest and a split skin graft was applied immediately to the raw surface. Early use of the arm was encouraged after the operation and the patients were out of bed within a week. The advantages of early activity are recognized and most of the patients are now ambulatory on the first postoperative day.

POSTOPERATIVE COMPLICATIONS

Table VI lists the postoperative complications of the 202 radical mastectomies. Three of the six deaths resulted from pulmonary embolism. One of the patients died while on the way home from the hospital, one died of a hemolytic streptococcus septicemia, one from active pulmonary tuberculosis and one from coronary thrombosis and a generalized peritonitis which resulted from the perforation of two acute ulcers of the colon.

TABLE 6.—*Surgical Complications in 202 Radical Mastectomies*

Complication	Cases	
Deaths	6	2.9%
Infected wound	18	8.8%
Hematoma wound	3	1.4%
Partial slough of skin flaps	34	16.8%
Edema of arm	26	12.8%
Limitation of motion of arm	6	2.9%
Pneumonia	3	1.4%
Thrombophlebitis	2	1.0%
Causes of deaths (all autopsied)—		
Pulmonary embolism	3	
Septicemia	1	
Pulmonary tuberculosis	1	
Cornary thrombosis, perforated ulcer of colon with peritonitis	1	

Most of the 34 cases listed as having sloughs of skin flaps had loss of small areas of skin, although some required secondary pinch or split grafts. In none of the 26 patients who developed swelling of the arm postoperatively was the edema severe enough to be disabling.

RECURRENCES

Although the majority of deaths from carcinoma of the breast result from widely disseminated metastases, especially to the lung, spine, pelvis and liver, we are especially interested in local and axillary recurrences. Table VII gives the incidence of regional recurrences in 149 cases followed more than five years after operation.

TABLE 7.—*Regional Recurrences in 149 Radical Mastectomies 1926 to 1941*

Site	Number	
Skin	24	16.2%
Axilla	14	9.4%
Supraclavicular	16	10.7%

A separate study was made of the sites of metastases in 375 cases, combining the cases treated by radical mastectomy alone with those receiving pre or postoperative x-ray therapy and those with recurrences who had been operated upon elsewhere. Table VIII gives the results of this study. The percentage of liver metastases is lower than that reported in autopsy series, probably due to the difficulty in palpating small nodules in the liver.

TABLE 8.—*Recurrences and Metastases in 375 Cases*

Site	Stanford 282		Recurrent 93	Total	
Lungs	62	22%	39	101	27%
Pelvis	49	20%	28	77	20%
Skin	27	9%	37	64	17%
Spine	38	13%	23	61	16%
Supraclavic	18	6%	25	43	11%
Ribs	20	7%	20	40	10%
Axilla	19	6%	20	39	10%
Liver	19	6%	5	24	6%
Pleura	11	4%	14	25	6%
Skull	7	3%	5	12	3%
Brain	9	3%	3	12	3%
Extremities	7	2%	2	9	2%

The clinical staging of the disease was important during the period of this series when Steinthal II cases were given heavy preoperative irradiation. It is well known that there is a large factor of error in the accuracy of the clinical diagnosis of axillary node metastases. Harrington[7] showed that 32 per cent of all patients with enlarged axillary nodes had no cancer within the axilla, while 29 per cent of those without clinically palpable nodes nevertheless had axillary metastasis. Haagensen and Stout[6] in their study of 622 radical mastectomies found that the clinical diagnosis was wrong in 15.1 per cent of clinical Stage I and 44 per cent wrong in clinical Stage II. Table IX shows the comparison of the anatomical as against clinical classification in this series.

TABLE 9.—*Anatomical vs. Clinical Classification**

Anatomical	Clinical (Steinthal)	
Stage I..... 90	Stage I..... 79 (15 were II)	
Stage II.....111	Stage II.....126 (26 were I)	
Stage III..... 4	Stage III..... 0 (4 were III)	
Anatomical I called Steinthal II.....26		28.9% error
Anatomical II called Steinthal I.....15		13.6% error

We were interested in seeing if our regional recurrences were any less in cases treated with pre or postoperative therapy. (Table X.) All regional recurrences are lower in postoperative irradiated cases, even lower than in our Stage I cases. Nodule recurrences are less in preoperative irradiated cases, but this series is quite small. Table XI gives our crude and net five-year statistics, irrespective of treatment. Of our five-year arrests, 31 per cent later had recurrences. Contrasted to our low overall survival figures are those with radical surgery alone. Here, 48.5 per cent is our lowest possible figure. Of course this is a select group in which only ten cases were in Stage III.

TABLE 10.—*Regional Recurrences in 140 Radical Mastectomics Followed 5 Years or Died with Carcinoma*

Anatomical Stage I.	Radical Mastect.	Preop. X-ray	Postop. X-ray	Total
Treatment cases	42	3	3	48
Skin	18 %	33 %	0	18 %
Axilla	4.4%	0	0	3.7%
Supraclavicular	0	0	0	0
Anatomical Stage II.	Radical Mastect.	Preop. X-ray	Postop. X-ray	Total
Treatment cases	35	10	25	70
Skin	20 %	20 %	12%	17 %
Axilla	17 %	10 %	12%	14 %
Supraclavicular	33 %	0 %	24%	22.4%
Anatomical Stage III.	Radical Mastect.	Preop. X-ray	Postop. X-ray	Total
Treatment cases	9	9	5	22
Skin	11 %	12.5%	40%	18 %
Axilla	0	12.5%	20%	9 %

TABLE 11.—*Five Year Survivals, 1926-1941*

	S.U.H. Only	Total Cases	Only Radical Mastect.
No. Cases	218	319	97
Total survival	84	102	52
Crude survival rate	38.5%	32.0%	53.6%
Net survival rate	41.2%	33.1%	60.0%
Total arrests	71	84	51
Crude arrest rate	32.5%	26.5%	52.2%
Net arrest rate	35.0%	27.2%	59.1%
Assuming all cases with radical mastectomy only who are lost, died with disease, crude arrest, is still			48.5%

Table XII breaks down our survival rates into anatomical stages. Our overall crude five-year arrest is 47.5 per cent in Stage II, our survival 56 per cent. Forty per cent of our arrests later had metastases. We further analyzed our cases to see how sub-groups in the same stage compared with each other. These results are net results.

TABLE 12.—*Analysis of Five Year Survival Rate*

	Stage I	Stage II	Stage III, IV	Recurrent
Cases	62	67	89	90
Crude survival rate	58.0%	56.5%	11.1%	31.0%
Net survival rate	64.1%	62.0%	11.8%	...
Crude arrest rate	53.1%	47.5%	6.7%	14.4%
Net arrest rate	59.0%	52.0%	7.1%	...
Per cent of 5 year arrests with later metastases	24.0%	40.5%	33.0%	100 %

Table XIII analyzes our Stage I. Our five-year results with surgery only could be better. The series treated with additional radiation are small and not significant. We expect Stage I to do well. The only value of bringing in our current cases here is for study of the trend. Some of these cases are only several months shy of the five-year goal.

All of them are at least nine months postoperative. We can yet hope this five-year group will do

TABLE 13.—*Five Year Survivals—1926-1941—Stage I*

	Cases	5 Year Survival	5 Year Arrest	5 Year Arrest with Later Metast.
X-ray only	5	2— 40%	1— 20%	0
Radical mastect.	42	27— 64%	27— 64%	7—26%
Preop. x-ray heavy	3	3—100%	2— 67%	0
Postop. x-ray	3	3—100%	3—100%	0
Simple mastect.	3	1— 33%	0— 0	0

better than the previous one. Table XIV analyzes our group in Stage II. In our ten cases treated moderately or heavily with preoperative irradiation we have only 20 per cent five-year cures. However, our cures, contrasting the surgical with the postoperative x-ray cases, shows those with surgery alone to have done better. True, this series is small. But, in our current group, of which over half have already gone three years, the best we can hope for is 57 per cent, and it is probable that the complete five-year total will not be over 50 per cent.

TABLE 14.—*Five Year Survivals—1926-1941—Stage II*

	Cases	5 Year Survival	5 Year Arrest	5 Year Arrest with Later Metast.
X-ray only	4	0	0	0
Radical only	35	24—68%	23—66%	11—48 %
Short preop. x-ray	5	2—40%	1—20%	0
Heavy preop. x-ray	5	2—40%	1—20%	0
Postop. x-ray	11	7—63%	6—54%	1—16.5%

CASES 1941—46

Radical Mastectomy	4	4—100 % living and well
Heavy preop. x-ray	1	1—100 % living and well
Postop. x-ray	33	19— 57.5% living and well
5 year arrest with surgery and surgery plus irradiation		55%

Table XV analyzes our Stage III and IV. Those treated with x-ray alone gave about 9 per cent survival. Twenty-seven of these were far advanced when first seen. All cases treated with primary surgery died soon. We can actually put both the simple and the radical mastectomies after heavy irradiation into the same group, as both of these groups were considered primarily inoperable, and operations was done only after the local lesion gave some evidence that it was no longer being controlled. These are our best results in Stage III.

TABLE 15.—*Five Year Survivals—1926-41—Stage III and IV*

	Cases	5 Year Survival	5 Year Arrest	5 Year Arrest with Later Metastases
X-ray only	66	6— 9.1%	1— 1.6%	0
Radical mastect.	9	0	0	0
Preop. x-ray heavy	8	4— 50.0%	2— 25.0%	0
Postop. x-ray.	0	0	0	0
Simple mastect. long after heavy irradiation	3	3—100 %	3—100 %	1—33%

Other small items of interest that came to light in this study are as follows:

1. Twenty-two of our patients had a history of some type of quack therapy before coming to us.

2. Twelve and seven-tenths per cent of our patients have a family history of cancer, but this is not always mammary cancer.

3. We could get no adequate history of estrogen therapy. Our cases receiving such therapy after operations were dead within a year. One case with a history of heavy estrogen therapy previous to surgery is arrested five years later.

4. Twenty-seven patients were prophylactically castrated. Five were without disease less than two years. Five were Stage I and without disease three years or over. Of the remaining 17, 12 had recurrences within 24 months. Eight of these latter cases were Stage II.

DISCUSSION AND SUMMARY

Under a policy of operating on all breast cancer in Stages I and II, and giving postoperative irradiation to those in which axillary metastases are found, the experience of the past 19 years has been analyzed.

Of Stage I so treated, 64 per cent were arrested for five years. The recurrences, early and late, were nearly half in the skin and more than a tenth in the axilla. This suggests that our criteria for staging were not followed rigidly enough and/or also that microscopic examination of the axillary nodes was not searching enough. Of the 44 Stage II cases given postoperative x-ray, only 11 have been followed five years, with 54 per cent of arrests. The group is too small to be dependable. Our present five-year group will do no better.

Before 1940 there were 35 Stage II cases treated by radical mastectomy only. A third of these recurred within five years, another third stayed well, but the last third went on to late recurrence. Our more recent cases given postoperative x-ray have not had time to reveal the full weight of such late recurrences. For a few years before 1941 we have a small experience of preoperative irradiation in clinical Stage II and selected Stage III (three proved after all to be only Stage I). Lumping the Stage II's and Stage III's together, the 21 cases yielded only seven five-year arrests (including three late simple mastectomies in cases initially well controlled by x-ray). These results are not good enough to make us try further any program of routine preoperative irradiation in Stage II. Stage III cases have given us only two five-year arrests in 75 cases (by x-ray irradiation) but many lived in fair comfort with their disease for several years (five of them for five years).

Skeletal metastases are frequent from cancer of the breast and can be a disaster for the patient, with severe pain and disabling fractures. The beneficient effect of x-ray in these cases has been to us outstanding. Many are temporarily restored to comfort and subjective health. We are also ready always to try x-ray and more x-ray on local and pulmonary and cerebral metastases. Liver metastases have responded less well, perhaps be-

cause of the sickness produced by significant x-ray dosage delivered in this region.

On the basis of this study we have discontinued the use of pre and postoperative irradiation in operable breast cancer. We continue to be very enthusiastic for the use of x-ray in holding incurable breast cancer in check and relieving the patient of the miseries of the disease for months and years.

CONCLUSIONS

1. Patients with carcinoma of the breast in Stages I and II should be treated by surgery only.

2. Those with recurrences should be treated by irradiation when the recurrence appears.

3. Cases in Stage III should all be treated by irradiation primarily.

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DDT—A POWERFUL WEAPON AGAINST INSECT-BORNE DISEASES

With the advent of DDT in the United States in 1943 a powerful weapon was launched against insect-borne diseases, according to an article in the November 2 issue of *The Journal of the American Medical Association.*

The author—Col. William S. Stone, M.C., Army of the United States—states that this insecticide will kill the anopheles mosquito which transmits malaria, the flea which transmits plague, the louse which transmits typhus and the fly which transmits dysentery and which may be a carrier of infantile paralysis.

Colonel Stone points out that "the nation now has within its grasp not only means to effectively control louse and flea-borne typhus fevers and the fly transmissions of the dysenteries but also improved methods for controlling malaria, leishmaniasis [a disease causing ulceration of the mucous membranes of the nose and throat], dengue [a fever], pappataci fever [also called sandfly fever] and filariasis. Progress has been made in controlling mite-borne diseases, and a lead has been obtained on how to control plague. There must be a continuation and extension of these efforts, and soon it should be possible for human beings to live in all parts of the earth without fear of insect-borne diseases."

DDT is manufactured in dry powder form, as a water-base spray and in a kerosenelike base. "In using DDT as an insecticide," the author writes that "it must be remembered that it is slow to act, with a knockdown varying from a few minutes to more than one hour; most insects showing evidence of DDT poisoning die, and its chief advantage over other insecticides is that on proper application to a surface it continues to be a potent contact insecticide for as long as three or four months. This latter property obviously has great significance in any insect control program."

In spite of the wide use of DDT and the poisonous effect it has on insects there have been "no clearcut cases of human poisoning" seen in the United States, according to Dr. Paul A. Neal of the National Institute of Health. Although a few persons have become ill, Dr. Neal said that it was due to the solvent or base and not to the DDT itself.

The compound, now commonly known as DDT, was first synthesized by a German chemist in 1874 and was patented as an insecticide in Germany in 1934. "In 1939," Colonel Stone states, "J. R. Geigy, Inc. of Basle, Switzerland, investigated its insecticidal properties for the control of clothes moths and certain agricultural pests. They also noted some of its residual insecticidal action after its application to a surface. During December of 1942 and early in 1943, studies conducted at the Bureau of Entomology, U. S. Department of Agriculture Laboratory at Orlando, Fla., confirmed the Swiss work and extended the information on the use of DDT as an insecticide with long lasting residual effect. This information was immediately applied to the development of materials and methods for the control of lice, mosquitoes, flies, fleas, sandflies, mites, bedbugs, cockroaches, clothes moths and many other insects of economic importance."

Its first use was to fight insect-borne diseases at the fighting fronts. The author concludes that "thus the necessity of war has contributed materially to peacetime living."

Diagnostic Problems in Luetic Cardiovascular Disease*

S. P. Lucia, M.D., and W. N. Sears, M.D., *San Francisco*

I. General considerations: The prevention of cardiovascular syphilis is the prevention of syphilis itself. In 1929 Bruusgaard[3] reported that of 473 patients who had received no anti-luetic treatment, 10 per cent had developed clinical evidences of cardiovascular lues. The average duration of syphilis in this group was 20 years. These data are in agreement with those of Turner,[17] who made a similar analysis of approximately 6,000 cases of late untreated syphilis at the Johns Hopkins Clinic. In 1937, Kemp and Cochems[4] reported an incidence of 12.7 per cent of cardiovascular involvement in a series of 1,000 luetics. There is abundant evidence in the literature to show that clinical involvement of the cardiovascular system will develop in approximately 10 per cent of untreated or inadequately treated cases of acquired syphilis. Post-mortem examinations reveal that in all instances where a pathological diagnosis of late syphilis can be established, 70-90 per cent of the subjects show evidences of cardiovascular lues.[5,18] Although these figures are based primarily upon microscopic changes, they serve to emphasize to the clinician the importance of being on the alert for signs or symptoms referable to the cardiovascular system in the patient afflicted with lues. From the very beginning syphilis is a vascular disease. Much has been written on the pathology of syphilis, particularly with respect to its protean manifestations, its predilection for the supravalvular portion of the ascending aorta, and its tendency to produce lowgrade inflammatory changes in the media and adventitia of the ascending, transverse, and less frequently, the descending limb of the aorta.[8] The earliest involvement of the aorta is due to lowgrade inflammatory processes in the adventitia and media of the ascending aorta not attended by gross anatomical alterations or symptoms. Secondly, there may be sufficient involvement of the elastica to account for dilatation of the aortic wall. Thirdly, there may be local destruction of the elastica followed by the formation of an aneurysm. Fourthly, the supravalvular portion of the aorta may undergo lowgrade inflammatory changes, with resultant fibrosis and scarring of the valve leaflets or there may be sufficient retraction of the valve leaflets to produce frank aortic insufficiency. Lastly, there may be narrowing of the coronary ostia as a result of the progressive fibrotic changes which have occurred in the walls of the aorta.

After varying lapses of time, these changes or any combination of them may follow the initial infection. In general it is believed that the diagnosis of cardiovascular syphilis becomes recognizable about 10 to 30 years after the primary infection. Furthermore, it must be remembered that approximately 50 per cent of the clinically detectable lesions of late syphilis are referable to the cardiovascular system.

The importance of establishing the diagnosis of luetic cardiovascular disease at the earliest possible time has been emphasized by several investigators,[9,10,12,16] and the effect of instituting early treatment is best summarized by Moore[8]:

The Incidence and Prognosis of Life Span in Patients with Various Types of Cardiovascular Complications in Late Syphilis.

Clinical Type	Percentage of Patients Affected	Prognosis Untreated	Prognosis Treated
Uncomplicated aortitis clinically unrecognizable	70-90	Good	Excellent
Uncomplicated aortitis, recognizable on basis of symptoms and signs	5-10	5-10 years	10-20 years
Aortitis with saccular aneurysm	1-2	1-2 years	5-10 years
Aortitis with aortic regurgitation	2-3	2-3 years	4-10 years

Many criteria have been given in order to evaluate the various signs and symptoms of uncomplicated aortitis.[1,2,7,10,11,13,14,15] The relative importance of these varies from observer to observer. In regard to the order of frequency and importance, uncomplicated luetic aortitis may be diagnosed when: (1) There is roentgenographic evidence of aortic dilatation; (2) The aortic second sound is hollow or of tambourr quality; (3) There is dyspnea; and (4) There is sub-sternal pain. In addition the patient should be under 40 years of age, free of hypertension, arteriosclerosis and other cardiovascular diseases which might produce identical signs and symptoms.[6] On the other hand the diagnosis of frank aortic insufficiency or of aneurysm seldom proves difficult.

II. Organization and Purpose of the Luetic Cardiovascular Clinic. In 1939, a special cardiovascular clinic for luetic out-patients was organized at the University of California. It was conducted by three full-time members of the medical staff in cooperation with the director of the clinic for luetics. Its purposes were to provide a diagnostic and advisory center, a uniform type of examination, a uniform type of record, and to make data available for teaching and research purposes. It was the intention of the group to give special consideration to the criteria suggested above and to determine to what extent it would be possible to make reliable diagnoses of early cardiovascular lues under the usual conditions found in

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an out-patient department. Ideally all patients who were seen in the clinic for luetics would be referred to the cardiovascular clinic and thus provide unselected material for statistical evaluation of diagnosis and treatment during the ensuing years.

The examination form used in the clinic was designed to obtain a complete cardiovascular history on each patient, with especial reference to the presence of pre-cordial pain, dyspnea, hemoptysis, cough, sputum, hoarseness, vertigo, edema, palpitation, indigestion, insomnia, weakness or other symptoms referable to the cardiovascular system. Space is provided on the form for the following special observations in the physical examination: the point of maximum intensity, the area of cardiac dullness (right border and left border), area of the base, thrills, murmurs, character of heart sounds including the aortic second sound, rate, character and rhythm of the pulse, blood pressure in each arm, and signs of arteriosclerosis. Provision is made for recording notes on the presence of the following: occlusion of peripheral vessels, episternal notch pulsation, diastolic shock, capillary pulsation, visible arterial pulsation and femoral pistol shot sounds. At the bottom of the form are listed the results of the teleoroentgenogram, fluoroscopy and electrocardiogram, followed by the diagnosis and recommendations for treatment.

At the completion of the examination, a working diagnosis was made, and recommendations for treatment were suggested to the staff in charge of the treatment of luetic patients. Adequate clinical follow-up was to be provided by scheduled return appointments for all patients examined in the luetic cardiovascular clinic.

III. Analysis of Data. During the five-year period covered by this study, approximately 2,000 patients were seen in the Luetic Clinic, and of these, 355 were given the cardiovascular examination as outlined in the special clinic. Therefore, it was impossible to make an accurate statement concerning the incidence of luetic involvement of the cardiovascular system in patients afflicted with syphilis. Those patients who were examined represented neither a random nor a selected sample of the population at risk.

In figures 1 and 2 are shown the age distribution of the patients seen in the luetic cardiovascular clinic. The majority of patients fell within the age group of 35 to 60 years. Of the total number of women, 71 per cent of the afflicted were over 40 years of age; and among the males, 85 per cent were over 40 years of age. Of the total afflicted subjects, less than one-third were women.

In figure 3 is given the number of sero-positive patients (132 or 34 per cent) in whom the diagnosis of no cardiovascular disease was made. The majority of these fell within the age group of 30 to 55 years. In general, those sero-positive patients having no cardiovascular disease tended to be younger than those sero-positive patients in whom the diagnosis of arteriosclerotic or hypertensive heart disease occurred (figure 4). The latter group comprised 114 cases or 29 per cent of the total. The major portion of these patients were between the ages of 45 and 65 years.

In figure 5 is demonstrated the incidence of the diagnosis of luetic cardiovascular disease of all types—136 cases or 35 per cent of the total. This graph demonstrates that in the age groups under consideration, luetic cardiovascular disease occurs most frequently in those age groups which also suffer from the highest incidence of arteriosclerotic or hypertensive heart disease. In other words, with rare exceptions, it is uncommon in this series of observations to find patients with luetic cardiovascular disease unaccompanied by

Luetic Cardiovascular Clinic ~ 1939 - 1944

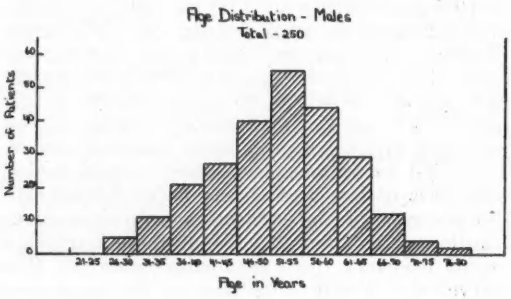

FIGURE 1

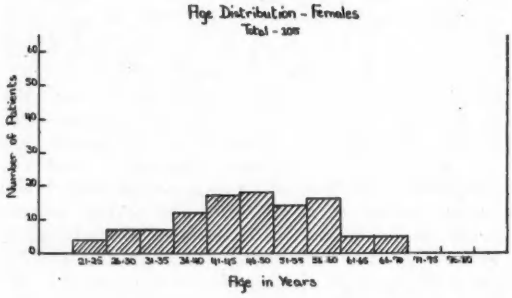

FIGURE 2

Incidence of Sero-Positive Patients
Diagnosed as Having No Cardiovascular Disease
Total: 132 cases ~ 34 % of 355 cases

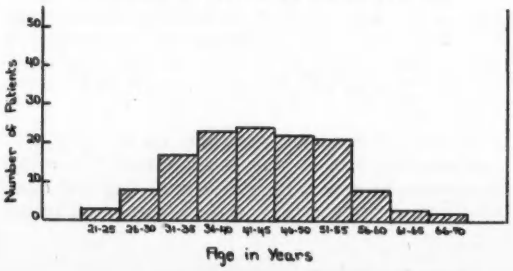

FIGURE 3

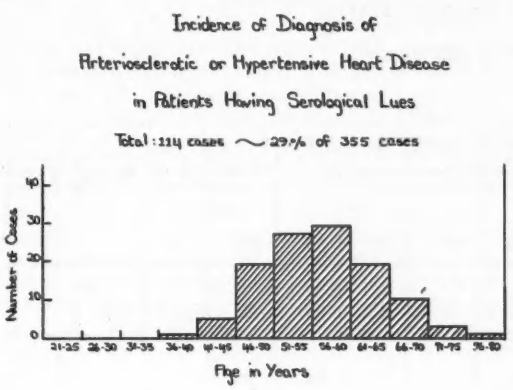
Incidence of Diagnosis of
Arteriosclerotic or Hypertensive Heart Disease
in Patients Having Serological Lues
Total: 114 cases ~ 29% of 355 cases
Number of Cases
Age in Years

FIGURE 4

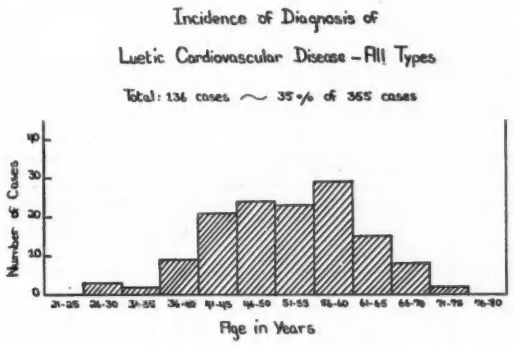
Incidence of Diagnosis of
Luetic Cardiovascular Disease - All Types
Total: 136 cases ~ 35% of 355 cases
Number of Cases
Age in Years

FIGURE 5

arteriosclerotic or hypertensive changes. As has been stated before, these latter changes may produce signs or symptoms which fulfill the criteria designated for luetic aortic involvement.

In Table I is recorded the distribution of diagnoses for the total group of 353 patients (one patient having been omitted because of congenital lues, and one because of a complicating mediastinal tumor). Since in many patients there was more than one diagnosis, the total number of diagnoses (388) exceeds the total number of patients (353). Of the total diagnoses 34 per cent are listed as having no cardiovascular disease; 29 per cent as having hypertensive or arteriosclerotic heart disease; and 35 per cent as having luetic cardiovascular disease—and of these 9 per cent luetic aortitis, 10 per cent aortic insufficiency, 16 per cent aortic aneurysm, and 2 per cent were listed as having rheumatic heart disease with mixed valvular lesions.

VARIETY OF CARDIOVASCULAR DIAGNOSES
IN GROUP UNDER STUDY - 353 PATIENTS

Diagnosis	Number of Cases	% of Total Diagnoses	
Luetic Aortitis	33	9	
Aortic Insufficiency	40	10	35
Aortic Aneurysm	63	16	
Mixed Valvular Disease	6	2	
Hypertension and/or Arteriosclerosis	114	29	
No Cardiovascular Disease	132	34	
Total Diagnoses	388		

Table I

In Table II is shown the age distribution of the three primary luetic cardiovascular diseases: aortitis, aortic insufficiency, and aortic aneurysm. It will be noted that the graver forms of luetic cardiovascular disease occur in the progressively older age groups and that the highest incidences occur after the age of 40 years. These data provide further evidence of the part which arteriosclerosis and hypertension plays in the onset of luetic cardiovascular disease.

In Table III is given the incidence of cardiovascular disease with respect to the time interval elapsing between the primary luetic infection and the date of observation. Of the total 355 subjects, 56 per cent had no knowledge of the date of infection, a figure in agreement with that of most observers. There appears to be very little difference in the interval of lapsed time between the primary infection and the onset of cardiovascular signs or symptoms in the group suffering from luetic cardiovascular disease when contrasted with the group suffering from arteriosclerotic or hypertensive heart disease.

It is possible that the incidence of cardiovascular disease, whether luetic, arteriosclerotic or hypertensive, may be a function of age rather than of duration of the infection. The exception to this statement appears to be in the group diagnosed luetic aortitis, where 18 per cent of the cases had a lapse of 11 to 15 years before the onset of cardiovascular symptoms. According to the criteria set down, aortitis is the most difficult to diagnose and hence the most likely to be over-diagnosed.

In Table IV the presenting complaints of all patients are listed according to diagnoses. As might be expected, those patients diagnosed as having no cardiovascular disease had fewer symptoms than those in the other diagnostic groups. The two most common complaints for all groups were dyspnea and chest pain, and these symptoms occurred more frequently in those patients who suffered from luetic cardiovascular disease.

In Table V the prominent physical findings of 347 patients are recorded according to diagnosis. Here again there have been multiple diagnoses on certain patients, and therefore the total number of diagnoses exceeds the total number of cases. Cardiac enlargement was observed in 39 per cent of patients having a diagnosis of aortitis, in 57 per cent with a diagnosis of aortic insufficiency, in 43 per cent with aortic aneurysm, in 25 per cent with arteriosclerosis or hypertension, and in 2 per cent of patients thought to have no cardiovascular disease. A tambour aortic second sound was encountered rather frequently in subjects suffering

AGE INCIDENCE OF LUETIC CARDIOVASCULAR DISEASE

TOTAL: 136 CASES - 35% OF 355 CASES

Diagnosis	No. of Cases	Percent of Cases by Age Group										
		21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75
Luetic Aortitis	33		3	3	12	21	18	15	18	9		
Aortic Insufficiency	40		5	2	8	12	20	20	12	12	8	
Aortic Aneurysm	63				3	14	16	16	29	11	8	3

Table II

INCIDENCE OF CARDIOVASCULAR DISEASE

WITH RESPECT TO INTERVAL ELAPSING FROM PRIMARY LUETIC INFECTION

Diagnosis	No. of Cases	Percent of Cases by Years Elapsed									
		1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	Unkn.
Luetic Cardiovascular Disease (All Types)	136	2	2	7	7	3	11	6	6	5	50
Luetic Aortitis	33	6	-	18	9	3	12	3	3	3	42
Aortic Insufficiency	40	2	2	5	5	5	8	10	5	8	50
Aortic Aneurysm	63	-	3	2	8	2	12	5	6	6	55
Arteriosclerosis and/or Hypertension	114	4	4	3	5	6	9	5	4	-	60
No Cardiovascular Disease	132	7	9	8	3	8	4	1	1	-	59
Total Diagnoses	382										
Total Cases	355	5	5	6	6	6	8	4	3	1	56

Table III

PRESENTING SYMPTOMS AND COMPLAINTS

Symptom	Percent Distribution by Diagnosis				
	Aortitis (33 Cases)	Aortic Insufficiency (40 Cases)	Aortic Aneurysm (63 Cases)	Arteriosclerosis and/or Hypertension (114 Cases)	No Cardiovascular Disease (132 Cases)
Dyspnea	76	50	54	40	30
Chest pain	39	32	46	20	11
Palpitation	36	42	36	29	17
Cough	21	17	25	2	9
Edema	3	10	10	1	7

Table IV

from aortic aneurysm, aortitis, and arteriosclerosis and hypertension. Eleven per cent of those having no cardiovascular disease were described as having a tambour aortic second sound. The "to and fro" murmur was found most frequently (75) in the cases of aortic insufficiency. In those instances where the "to and fro" murmur was observed in patients with aortitis, a coincidental diagnosis of aortic insufficiency was also made. The aortic systolic murmur has been established as one of the criteria for the diagnosis of luetic aortitis. In this series of observations, the aortic systolic murmur occurred in 30 per cent of patients diagnosed as having luetic aortitis, in 36 per cent diagnosed as having aortic aneurysm, and in 33 per cent diagnosed as having arteriosclerosis or hypertension. It is clear, therefore, that the use of this isolated clinical finding as a means of differentiation between those conditions is not sound. Moreover, 8 per cent of patients who had no demonstrable cardiovascular disease exhibited an aortic systolic murmur as an isolated finding. Signs of arteriosclerosis were evident in a high percentage of all cases except in those having no cardiovascular disease. A dilated aorta was noted fluoroscopically in 60 per cent of the patients diagnosed as having aortitis, in 52 per cent of those with aortic insufficiency, in 62 per cent of those with aneurysm, and in 64 per cent of patients with arteriosclerosis or hypertension. These data render this isolated sign of doubtful pathognomonic significance for any single diagnostic category. During the period of observation there were differences of opinion as to the presence or absence of a dilated aorta, whether or not the aortic second sound was of tambour quality, and whether or not these changes were due to arteriosclerosis or lues, or in some instances to hypertension.

Fifty-five patients were given yearly cardiovascular examinations while under treatment and in none of these was there demonstrated any regressive changes in the cardiovascular status.

COMMENT

In a group of 355 patients observed in a luetic cardiovascular clinic, the age distribution was such that arteriosclerotic changes in the cardiovascular system made the diagnosis of early luetic aortitis practically impossible. The objective criteria for the diagnosis of luetic aortitis may also be fulfilled by hypertensive and arteriosclerotic heart disease without lues, and unless these conditions can be eliminated, the diagnosis of uncomplicated luetic aortitis under average circumstances cannot be made with any degree of assurance. The prevention of the cardiovascular complications of lues is best accomplished by the early adequate treatment of the primary infection.

CHIEF PHYSICAL FINDINGS
Total Cases 347

Physical Signs	Percent Distribution by Diagnosis				
	Aortitis (33 Cases)	Aortic Insufficiency (40 Cases)	Aortic Aneurysm (63 Cases)	Arteriosclerosis and/or Hypertension (114 Cases)	No Cardiovascular Disease (132 Cases)
Cardiac Enlargement	39	57	43	25	2
Tambour A_2	39	17	44	33	11
Aortic Murmur: To and fro	33	75	21	2	-
Systolic	30	-	36	33	8
Diastolic	12	25	6	2	1
Signs of Arteriosclerosis	70	68	63	100	19
Dilated Aorta	60	52	62	64	5

Table V

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Physiology of Traumatic Reflexes and Respiration During Surgical Anesthesia*

OBSERVATIONS MADE UNDER PENTOTHAL AND LOCAL NERVE BLOCK

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THIS report is based on a succession of clinical observations made during the past two and a half years, in which time the combined use of intravenous pentothal sodium and local nerve block provided the anesthesia of choice for 70 per cent of general surgical cases. Admittedly this present work reflects the viewpoint and perspective of the surgeon. For this reason the indulgence of the professional anesthetist is asked for any gross shortcomings in the accompanying interpretation of physiologic phenomena. The facts, nevertheless, are distinct and stand by themselves.

There is, however, a certain advantage in the surgeon's approach to the problem of the physiology of surgical anesthesia. The surgeon is in a position to continue and project into this clinical field his background of training in experimental physiology; he may at once initiate, observe and record variations in physiologic response to surgical trauma; he may at will functionally denervate with injections of procaine, selected neurogenic areas, thus eliciting contrasting physiologic responses from which he may bring evidence to bear on the problem of specific pathways of nerve impulse conduction. With these potentialities at hand, the surgeon should contribute largely to the basic problem of the physiology of surgical anesthesia.

The introduction of intravenous pentothal sodium anesthesia by Lundy a decade ago contributed not only a new agent of great value, but it provided also a new opportunity for the study of the physiology of surgical anesthesia. This enlarged opportunity is based on the selective pharmacologic action of the drug. Pentothial sodium exerts its major depressing effect on the cerebral cortex and on the thalamus. It thus in effect establishes a functional decerebration of the surgical patient. The physiologic status of the patient under pentothal sodium anesthesia is quite comparable from the viewpoint of reflex studies, to the surgically decerebrated animal. By virtue of this restricted primary local pharmacologic action at and above the level of the thalamus, all reflex arcs between the vital centers in the bulb (i.e., respiratory center) and the periphery remain intact. The additional graded depressing action of this drug on the respiratory center in the medulla, and its concomitant lack of action on the conduction pathways of the nervous system below the bulb, create a unique opportunity for accurate estimation of the interrelationship existing between peripheral traumatic stimuli of surgical origin and observable respiratory responses.

This situation with pentothal anesthesia stands in sharp contrast with the condition prevailing under ether anesthesia. With ether the conduction pathways distal from the bulb are depressed even to the point of establishing paralysis in the areas of distribution of the intercostal nerves. Also the local irritation of the air passages by ether fumes initiates afferent impulses in the pulmonary vagal reflex arcs which strongly stimulate respiration and distort completely the picture of simple traumatic reflex stimulation of respiration. Spinal anesthesia by its massive point suppression of afferent impulses at the juncture of the peripheral nerves with the spinal cord, eliminates all possibility of central conduction of nerve impulses of peripheral origin, thus abruptly terminating any possibility of studying such reflex actions. Regardless of the opinion which one holds concerning the value of pentothal sodium as a general anesthetic agent, the drug does provide an approach to the study of the physiology of anesthesia during the course of surgical procedures which is not equaled by any other anesthetic agent.

The identification of surgical trauma as the

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principle causative factor in the reflex stimulation of respiration during surgical procedures which stems from this study, is in accord with the recent emphasis placed by many students on the importance of the neurogenic control of respiration as contrasted with its chemical control. The present study may be said to extend the observation made by the Swedish anesthetist Gordh to the effect that the physiology of respiration dominates the physiology of anesthesia. From this present study a more comprehensive concept may be enunciated to the effect that, disregarding the problem of pain control and of muscular relaxation, the physiology of surgical anesthesia resolves itself into the question of the momentary balance between the reflex stimulation of respiration by afferant pain impulses of traumatic origin and the depressing effect of the anesthetic agent on the stimulated respiratory center. This balance will be distorted or altered by the specific stimulating effect of inhalation anesthetic agents on the pulmonary vagal reflex arcs, or by the specific depressing action of an anesthetic agent on the conduction pathways of the nervous system distal to the bulb (ether, cyclopropane and spinal procaine).

METHOD

Two general approaches were utilized in the present effort to unravel the physiology of surgical anesthesia. First, a series of quantitative studies were carried out based on the rate of utilization of pentothal per minute in 200 major surgical procedures in which a detailed record of utilization and of other pertinent data was accurately kept. This group was supplemented by an additional group of 200 to 300 selected cases bearing on specific problems noted in the analysis of the original 200 cases. Analysis of the rate of utilization of pentothal per minute was made with reference to age, sex, weight, length of operation, type of operation, and the effect of procaine block interruption of afferent nerve impulse conduction. The record of the rate of utilization per minute was kept in blocks of ten-minute periods for the entire surgical episode. Such charting of the rate of utilization in blocks of ten minutes makes possible an accurate correlation between changes in the rate of utilization of pentothal and sources of surgical trauma during the progressive technical phases of an operation.

The second method of study was that of pneumographic recording of specific responses by the respiratory mechanism to controlled selected types of surgical trauma. By use of pneumograms the intensity and the specific characater of the respiratory response could be precisely analyzed with reference to the anatomic plane or the neurologic field of origin of the stimulating surgical traumata. Procaine blockage of afferent nerve impulses again verified the assumption of a causal relationship between specific forms of surgical trauma and respiratory stimulation by obliterating in the pneumograms the specific respiratory responses.

QUANTITATIVE STUDIES

An analysis of the rate of utilization of pentothal in the 200 successive detailed cases showed that the two most important factors bearing on the rate of utilization of the drug are the duration of the operation and the type of the operation. When proper adjustment was made for the factor of duration as between long operations (over an hour) and short operations (under one hour), the factors of weight, sex and age had no important bearing on the rate of utilization of the drug. The single exception to this generalization is that there did appear to be a distinct reduction in the rate of utilization of the drug after 60 years of age.

The importance of the duration of an operation on the rate of utilization of the drug appears to be related to two facts: first, to the proportionately greater weighting of the averages for short operations by the initial, large induction dose than would occur in the averages for long operations in which there would be a greater dilution of the weighted value of the large induction dose by the longer time factor; second, to the decreasing reflex stimulation of the respiratory center from trauma in long major operations, in which increasing numbers of pathways of nerve conduction are severed, thus causing a progressive diminution in the number of afferent impulses conducted centrally from the field of operation to the respiratory center.

The type of operation is important in determining the rate of utilization of the drug because of the varying intensity of the afferent neurogenic impulses initiated by trauma in the different anatomic areas. Reflex stimulation of respiration from trauma in the lumbar and sacral regions during pelvic operations is minimal, as contrasted with the maximal stimulation of respiration by reflexes initiated in the subdiaphragmatic region during surgery of the stomach or gall bladder.

The first comparative study of the rate of utilization of pentothal before and after the interruption of afferent nerve impulses by procaine nerve block was made during two series of operations on the gall bladder and ducts. The first series in which a study of the rate of utilization of pentothal was made were all performed under pentothal action alone, so that all reflex arcs between the periphery and the respiratory center were intact. The increased need for pentothal to control the stimulation of respiration from traction on the gall bladder was apparent to both the surgeon and the anesthetist and borne out by charts and averages. The second series was performed after establishment of anterior splanchnic block anesthesia as a supplement to the already established pentothal anesthesia. The splanchnic block interrupted the afferent visceral sensory impulses initiated by traction on the gall bladder, and reduced the reflex stimulation of respiration in a manner clearly apparent to the surgeon and anesthetist and again borne out by the charts (Chart 1) and figures. The diminution of respiratory stimulation was paralleled by a sharply reduced rate of utili-

Type of Operation	Number of Cases		Rate of Utilization - Gms./Min.	
	Pentothal Alone	Pentothal and Block	Pentothal Alone	Pentothal and Block
Cholecystectomy	22	22	0.033	0.019
Gastric Resection	3	3	0.039	0.011
Right Hemicolectomy	2	2	0.014	0.006
Radical Breast	4	6	0.023	0.013

CHART I.

zation of pentothal as is reflected in the 50 per cent reduction in the rate of utilization of pentothal per minute after splanchnic block. In the first series of operations done under pentothal anesthesia alone, the rate of utilization of pentothal was 0.033 gm. per minute; in the second series in which pentothal anesthesia was supplemented by anterior splanchnic block with procaine, the rate of utilization was nearly halved to the figure of 0.019 gm. per minute. A second comparable study was made by supplementing pentothal anesthesia with procaine intercostal nerve block for radical mastectomy. Again two series were run. In the first group of cases operated on under pentothal anesthesia alone so that all reflex arcs between the respiratory center and the periphery were intact, the rate of utilization of pentothal was 0.023 gm. per minute. In the second series, in which pentothal anesthesia was supplemented by intercostal nerve block which interrupted all afferent impulses so that they did not reach or stimulate the respiratory center, there was a sharp reduction by nearly a half in the rate of utilization of the drug per minute to the figure 0.013 gm. In several instances a cholecystectomy or a radical mastectomy was performed when supplemental procaine nerve block (splanchnic or intercostal) was used, without the need of administering any further pentothal after the initial induction dose.

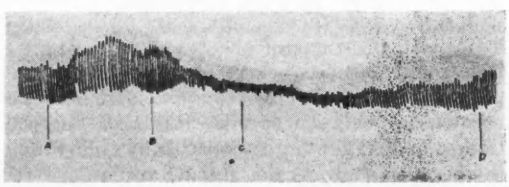
PNEUMOGRAPHIC OBSERVATIONS

A systematic study of reflex activation of respiration from surgical trauma, which is clearly apparent by observation alone, was made with pneumographic studies of low intercostal (thoracic) respiration. This level provides the best recording of the all important expiratory phenomena of respiratory stimulation. The results of these recordings may be reviewed quickly under the following headings: (A) Pentothal Effect; (B) Traumatic Reflex Stimulation of Respiration; (C) Neurospecific Segmental Reflex Responses (cervical, thoracic, lumbar, sacral).

A. Pentothal Effect. The crux of pentothal effect in third stage anesthesia—assuming an absence of traumatic reflex stimulation of the respiratory center—is a smoothly graded depression of respiration. This effect is measured on a pneumogram as a curve with gradually diminishing amplitude which measures the decreasing volume of respiration. There is practically no alteration in the volume of respiration at a constantly maintained level of pentothal anesthesia as shown by Graph No. 1. The characteristic uniformity of the pattern of respiration is impressive. In this and in all subsequent graphs, inspiration is recorded by the downward stroke of the pen, while expiration is recorded by the upward stroke of the pen.

Graph No. 1.—Induction of anesthesia with pentothal.

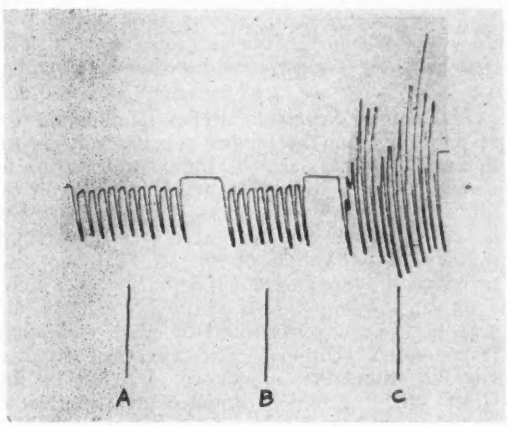
Graph No. 2 shows, after an initial basic run of unstimulated respiration to A, a mild stimulation of respiration from the trauma of an incision made in a reflex area of low intensity. This is manifested by an increase in the amplitude of respiration. The administration of 40 cc. of 1 per cent solution of pentothal in successive fractions of 10 cc. amounts, given with a minute interven-



Graph No. 2.—Pentothal action during surgery.

ing between the fractions (after B), represses the reflexly stimulated respiration as the surgical procedure advances, until the amplitude of respiration is definitely reduced. As the drug is progressively metabolized, respiratory amplitude is gradually restored to fuller volume (after C). The depth of anesthesia, nevertheless, is still adequate to control significant traumatic reflex stimulation of respiration.

B. Traumatic Reflex Stimulation of Respiration. This whole body of research is based on the premise that traumatic or painful impulses are conducted centrally in the anesthetized patient, and that they impinge upon and stimulate the respiratory center; that they do not ascend higher during third stage pentothal anesthesia, because they are blocked by the specific action of pentothal at the level of the thalamus. Graph No. 3 is presented to substantiate this basic premise. The tracing is made with three distinct runs of the pneumograph. The first run (A) was made under pentothal anesthesia prior to any surgical trauma. It exhibits the usual type of curve. The second (B) and third (C) runs were made while making an abdominal incision the upper half of which, only, was carefully procainized by subcutaneous and intracutaneous infiltration with procaine. The contrast between the respiratory response to incising the upper injected and lower uninjected halves of the incision is striking. Under exactly the same conditions of anesthesia and trauma except for the peripheral suppression of painful impulses in the upper half of the incision by procaine infiltration, there is a completely different respiratory response. The second run, recorded while making the incision in the upper procainized half, shows a stable unvarying type of respiratory curve identical to that seen in the first run under anesthesia alone. The third run, recorded while

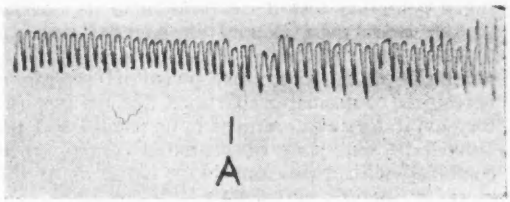


Graph No. 3.—Traumatic reflex stimulation of respiration.

making the incision in the lower uninjected half, exhibits the characteristic reflex stimulation of respiration particularly on the expiratory side, which typifies the response to surgical trauma in this part of the body.

C. Neurospecific Segmental Response (Cervical, Thoracic, Lumbar, Sacral). Characteristic and differing patterns of respiratory response are demonstrable following trauma in each of the four major neurologic regions of peripheral nerve distribution. By and large the same pattern of response is noted in a particular neurologic segment whether the site of trauma for the particular neurologic region is in the somatic zone (cerebrospinal nerve conduction) or in the visceral zone (visceral sensory autonomic nerve conduction).

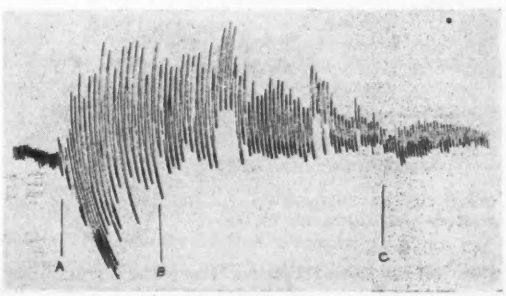
1. Cervical Segment. For the most part there is little evidence of reflex stimulation of respiration by trauma in either the somatic or visceral regions of cervical nerve distribution. Graph No. 4 shows first a normal run without trauma, and in the sec-



Graph No. 4.—Cervical somatic.

ond part (A) the minimal respiratory stimulation associated with making a skin incision in the neck for thyroidectomy. Trauma in the visceral zone shows a complete absence of significant stimulation of respiration during the clamping and resection of the thyroid gland.

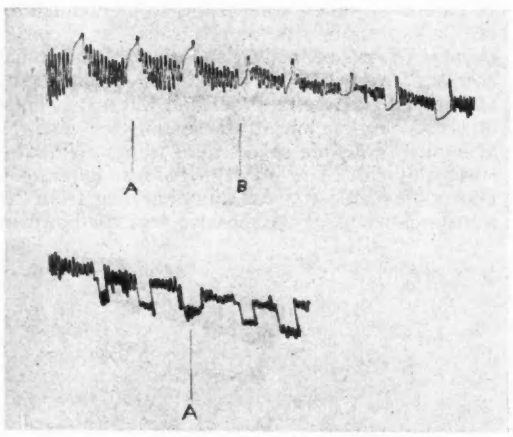
2. Thoracic Segment. From the thoracic segment (intercostal nerves) which covers the area from the base of the neck to the symphysis pubis come the most arresting manifestation of reflex stimulation of respiration by surgical trauma. This is of great importance because the manifestations of reflex stimulation is predominantly on the expiratory side of respiration as a consequence of reflex activation of the abdominal accessory muscles of respiration (transversus abdominis, and the external and internal oblique muscles). Activation of these muscles disturbs abdominal quietude so essential to a satisfactory surgical field. The most vigorous expiratory efforts are manifest from stimuli arising from the somatic portions of the thoracic area as shown in



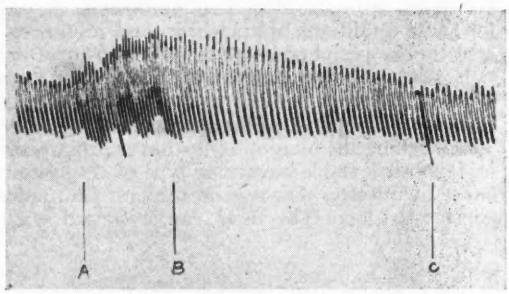
Graph No. 5.—Thoracic somatic.

Graph No. 5. After an initial run with moderate amplitude before any surgical trauma is instituted, there appear sudden explosive respiratory cycles immediately upon starting an incision (A). Although there are a few initial inspiratory downstrokes of considerable magnitude, these are quickly followed by a succession of expiratory upstrokes of excessive amplitude (B). These result from a marked prolongation and intensification of expiration due to forceful reflex contraction of the accessory abdominal muscles of respiration which pull on the lower rim of the thoracic cage. This shift distorts the normal inspiratory-expiratory ratio of 1 to 1, over to the abnormal ratio of 1 to 5 or 10. This reflex activation of respiration is quickly controlled upon fractional administration of additional amounts of pentothal as shown in the latter half of the graph. The additional pentothal restores expiration to its normal passive character (C), and the lateral abdominal muscles are inactivated (not paralyzed). The amplitude of the expiratory phase of respiration is restored to normal proportions, and the inspiratory-expiratory ratio returns to its usual 1 to 1 relationship. This state of pentothal control when combined with a procaine block paralysis of the rectus abdominis muscles, provides an ideal state of abdominal quietude for surgical purposes.

The respiratory response to trauma in the visceral portions of the thoracic region is of a more complex character. This probably is related to a mixed innervation for the visceral regions derived from the sympathetic and vagal sources, and possibly somewhat in the upper abdomen from the phrenic sources. In a sufficiently light plane of pentothal anesthesia the predominance of the expiratory response to trauma is still demonstrable. Prolonged expiratory arrest both for the intercostal and diaphragmatic components of respiration from traction on the pyloric end of the stomach has been recorded. The same phenomenon of expiratory arrest under pentothal anesthesia was also induced by traction on the gallbladder during a cholecystectomy. The next Graph, No. 6, is a recording which follows immediately on the establishment of an anterior splanchnic nerve block with procaine. After three episodes of expiratory arrest from traction on the gallbladder (A), infiltration of the procaine causes these to disappear and the phenomenon is altered. The traction respiratory phenomenon is converted into a phase of inspiratory arrest of respiration (B). In the next line, taken after the passage of more time, there is still a downward curve indicating transfer of the thoracic cage to the position of inspiration, but there is no longer complete arrest of intercostal respiration. Increasingly the curves of intercostal respiration although of lessened amplitude, become superimposed on the inspiratory phenomenon of traction (A). As a consequence the upward forceful retraction of the liver and gallbladder by the diaphragm into the deep recesses of the abdomen during expiration, which is the principal handicap of pentothal anesthesia during upper abdominal surgery, is nullified. The liver and gallbladder swing easily downward and out into the incision, providing an ideal field for surgical procedures on the biliary passages. To accomplish this effect with pentothal alone would entail entering undesirably deep planes of pentothal anesthesia.



Graph No. 6.—Thoracic visceral. Splanchnic block. Expiratory and inspiratory arrest.

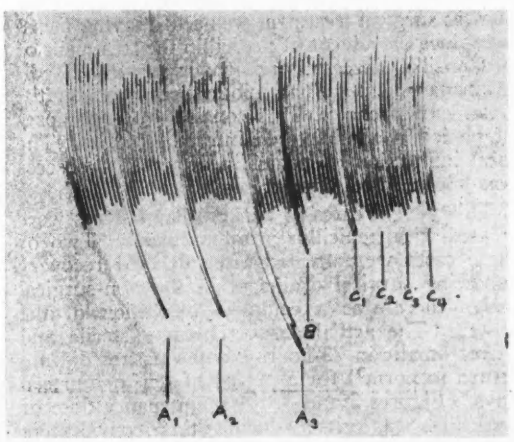


Graph No. 7.—Lumbar visceral. Procaine block.

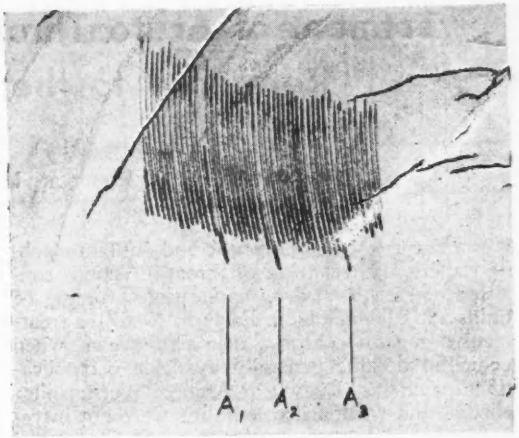
3. Lumbar Segment. Reflex stimulation of respiration from the lumbar somatic zone is of minimal intensity, and of little surgical significance. There is usually a gentle stimulation of the amplitude of respiration. Importantly there is no activation of the accessory abdominal muscles of expiration, so that there is no disturbance of abdominal quietude during operation. This gentle stimulation is frequently entirely absent, and is easily controlled by small additional fractions of pentothal. The effect of lumbar visceral stimulation is shown dramatically in Graph No. 7. After an initial control run without trauma following surgical exposure of the presacral (superior hypogastric) plexus of nerves, the plexus was traumatized (A to B) and subjected to traction with a thumb forceps. There is an immediate increase in the rate and amplitude of respiration. Then procaine solution was injected above the point of continuing trauma to the plexus (B). The immediate effect of the block was that the rate of respiration was quickly re-

duced. Subsequently the amplitude decreased more gradually, but just as definitely. Following complete surgical severance of all the presacral fibres at the dark line (C), as the initial step in a presacral neurectomy, a marked yet stabilized reduction both in the rate and amplitude of respiration occurred.

4. Sacral Segment. The area of sacral nerve distribution provides an interesting type of reflex stimulation of respiration by trauma. Again in the sacral area the respiratory response is identical in the somatic (cerebrospinal) and visceral (autonomic) zones. The response to trauma in this area consists of a single prolonged inspiratory effort associated with a distinct moaning phonation from reflex laryngospasm. In the visceral zone with autonomic sacral nerve distribution, the reflex was elicited by traction on the uterus which produces tension in the cervicovaginal region at the point of juncture with the utero-sacral ligaments. The significance of the utero-sacral ligaments as the source of this reflex was demonstrated by cutting the entire cuff of the vagina away from the cervix except at the point of attachment of the utero-sacral ligaments. With this restricted area alone intact, the reflex persisted in full force with repetition of traction. Injection of the utero-sacral ligaments with procaine promptly obliterated the reflex. Subsequently in several instances where the reflex was encountered prior to beginning a hysterectomy, it was obliterated by injecting the utero-sacral ligaments with procaine solution. The utero-sacral ligaments have consequently been identified as a pathway carrying afferent fibers from the sacral plexus of autonomic nerves (inferior hypogastric plexus) which transmit impulses centrally as a result of surgical trauma so as to stimulate inspiration and induce a reflex laryngeal phonation. The relationship of this reflex to the sacral plexus is demonstrated in Graph No. 8. Here three sharply prolonged inspiratory efforts were induced by separate tractions on the utero-sacral ligaments. (A_1, A_2, A_3). Each inspiration was associated with a moaning laryngospasm. At the dark line on the graph (B), while the recording was interrupted, a deep presacral injection of procaine in the region of the inferior hypogastric plexus was made. Following the injection traction was again exerted several times (C_1, C_2, C_3, C_4). In only the first instance of traction was a feeble disappearing inspiratory response demonstrated. Following this single feeble response there was a complete obliteration of all further reflex stimulation of respiration by traction.



Graph. No. 8.—Sacral visceral. Pentothal anesthesia. Procaine block.



Graph. No. 9.—Sacral visceral. Ether anesthesia.

A growing familiarity with these reflex patterns led the author to watch for evidences of them while working under anesthesia with other agents. Ample evidence could be noted that the same pattern of reflexes prevailed, although partially obscured, with the other agents. Under spinal anesthesia even as high as the third interspace, the visceral traction reflex from the gallbladder occasionally produced unendurable pain and respiratory distortion—even expiratory, arrest, due undoubtedly to the entrance of impulses over the splanchnic sympathetic fibers into the cord at the second or first thoracic levels, which is known anatomically to occur. Infiltration of the mesentery around the cystic and common duct region eliminated this painful reflex. Under ether anesthesia during the second stage, the prolonged vigorous expiratory effort from reflex activation of the abdominal accessory muscles of respiration was frequently observed. Finally a clinching bit of evidence that these reflexes underlie the whole field of surgical anesthesia with all anesthetic agents is presented in Graph No. 9. This graph, made during a hysterectomy at a point under deep, third stage ether anesthesia, shows three typical prolonged inspiratory efforts associated with reflex moaning laryngeal phonation (A_1, A_2, A_3) from traction on the uterus and on the utero-sacral ligaments. The validity of this whole study as an exposition of the basic reflex patterns in back of the physiology of surgical anesthesia appears therefore to be substantiated.

Treatment of Acute Throat Infections, With Special Reference to the Use of Penicillin*

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PRIOR to chemotherapeutic and antibiotic substances, the treatment of throat infections consisted of rest, local drug applications, forcing of fluids and alkalinization. Early in 1945, the treatment began to take on a new significance, when penicillin became generally available. Complications such as Ludwig's Angina, peritonsillar abscess and peritonsillar cellulitis were not infrequent and when these appeared, severe illness and occasional fatalities resulted. This paper is presented to show the specific therapeutic role which the sulfa drugs and penicillin play in the treatment of acute throat infections. A military hospital has proved ideal, for observation, isolation, availability and otherwise suitably controlled studies on groups of patients. In the later months of 1945 and early 1946, a total of 561 cases of throat infections were treated. These were divided into certain groups (Figure 1), acute exanthemata (scarlet fever), acute tonsillitis, acute pharyngitis, monilia (rare), Vincent's Angina, peritonsillar cellulitis and abscess, and Ludwig's Angina.

During this period of observation, 2,212,800,000 units of penicillin were administered to all types of cases. This amount gave a first hand opportunity to explore the efficiency of the drug in a large variety of conditions and to note the effect of all dosage scales and routes of administration, as well as blood and body fluid levels, response to therapy, relapses, and the development of penicillin resistance.

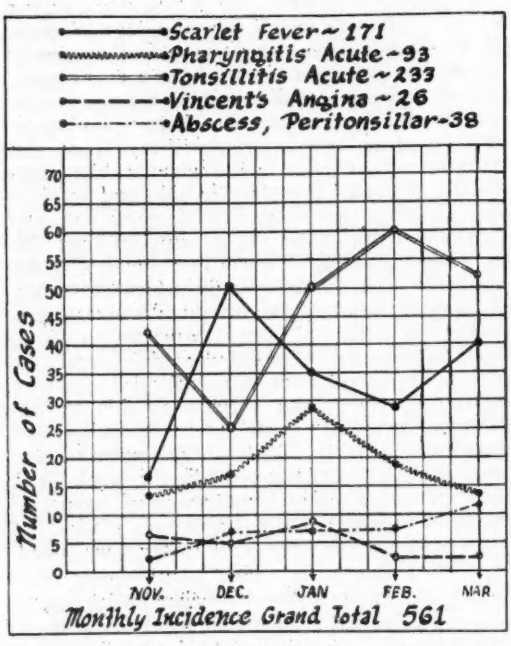


Fig. 1.—Incidence and distribution chart of the series of throat infections studied.

* Read before a combined meeting of the San Diego County Medical Society and the staff of the U. S. Naval Hospital, San Diego, April 9, 1946.

THE USE OF PENICILLIN

No rule can be applied to all cases in the use of penicillin, as the success of treatment depends on the sensitivity of the primary invading organism, the presence of secondary invaders and the resistance of the patient.[15] The bacteriological study of the infecting organism prior to the institution of treatment is ideal. When dealing with acute fulminating infections, acute infections and contagious diseases with high morbidity rates, of complications, treatment should be instituted without waiting to obtain the results of preliminary bacteriological studies. Sensitivity tests in our experience did not seem warranted unless the case was resistant to the instituted therapy. An evaluation of the sensitivity of the invader was indicated, before stopping or prolonging, or increasing the amount of the drug.

PERITONSILLAR ABSCESS

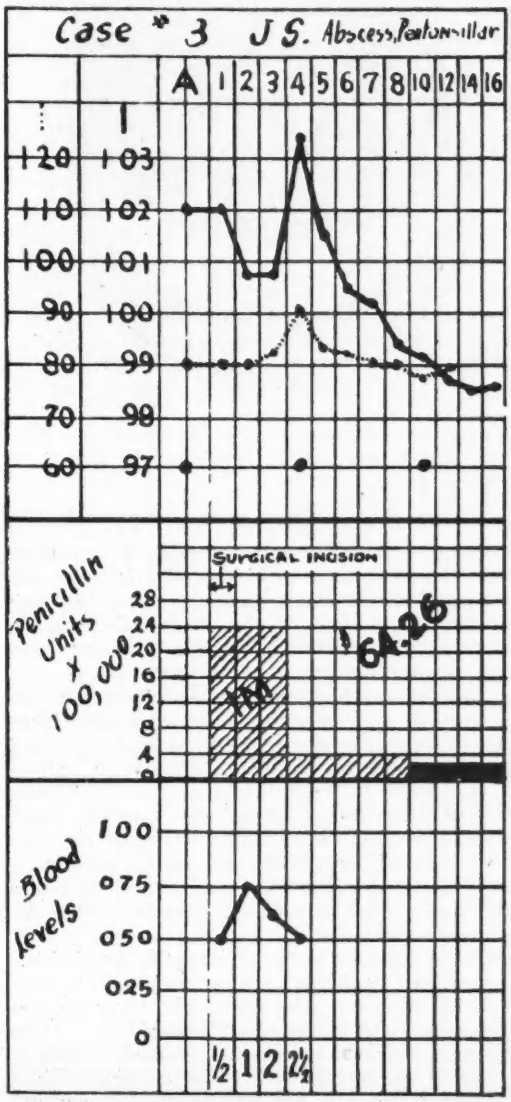
Peritonsillar abscess has long been considered a surgical disease. Treatment consisted almost entirely of lancing and draining. This method usually gave good end results. It had a morbidity of prolonged illness, pain and discomfort, frequent delayed resolution, a high relapse rate and it was not without hazard. Although in many instances surgical treatment was a life saving measure, since the advent of penicillin the treatment of peritonsillar abscess is no longer surgical. Medical management with antibiotic therapy is now the treatment of choice. This consists of large doses of penicillin administered intramuscularily.[9] The local infiltration of penicillin around the abscess was tried and results were equivocal.[8]

Thirty-eight cases of peritonsillar abscess were treated with penicillin intramuscularily. Two of these cases were treated after delayed recovery following surgical drainage. In the non-surgical group there was a complete resolution of the abscess. The actual abscess became sterile and asymptomatic in 72 hours but the tissues did not return to normal for a period of ten to fourteen days. (Figures 2 and 3.) A maintenance dose of penicillin was given during this convalescent asymptomatic period. Penicillin during this convalescent period was necessary to prevent relapse.

After recovery was complete, throat and tonsils returned to a normal appearance. Tonsillectomies were not advised at this time. A period of one to three months was allowed to elapse before elective surgery was recommended.

THE CONCURRENT ADMINISTRATION OF SULPHONAMIDES AND PENICILLIN

The concurrent administration of sulfonamides and penicillin in adequately large doses,[16] is advocated for the desperately ill patient. The blending of two or more chemotherapeutic agents or antibiotics, as with anesthetic agents, known as "balanced therapy" produced an efficient result. This balance is brought about when penicillin and sulfonamides are combined. In addition to a specific effect on a common organism, each has an individual specificity. This broadens the scope of action in preventing complications and terminating infection. Other agents or measures may be combined to produce balanced therapy, such as hyperthermia and local applications to remove inhibitory substances[15] such as penicillinase. This principle of balanced therapy has been used when the patient's life was at stake, or unusual resistance was manifested.



Feg. 2.—Peritonsillar abscess: Surgical incision made on first hospital day. Intramuscular penicillin is represented by diagonal lines—Oral penicillin by solid black.

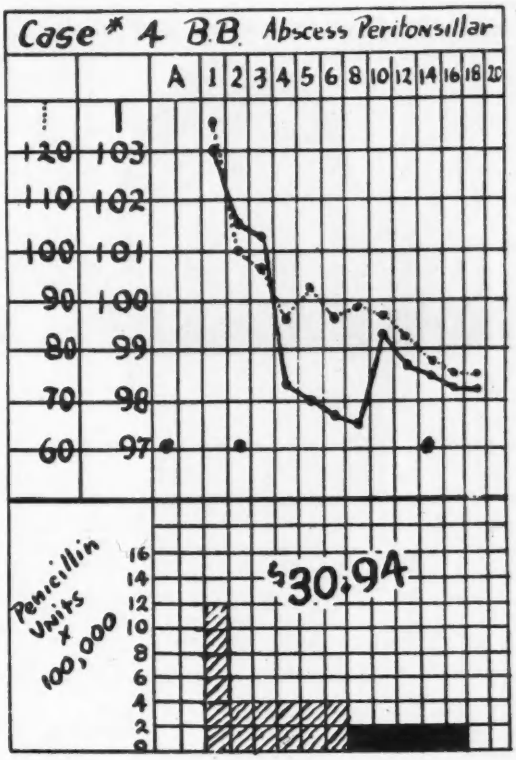


Fig. 3.—Peritonsillar abscess: No surgery. Note prompt response to penicillin therapy, both intramuscularly and orally and compare with Fig. 2.

Ludwig's Angina (Figures 4 and 5), acute severe peritonsillar cellulitis with early abscess, lobar pneumonia, meningococcic meningitis, pneumococcic meningitis and certain other overwhelming infections of coccal and spirochetal origin are examples of serious infections requiring such balanced therapy. Excellent results have been obtained in a large number of cases from the concurrent administration of large doses of penicillin (probably G fraction) by the intramuscular route (100,000 units every hour) or occasionally by the intravenous route, and by intravenous sulfonamide diluted in one-sixth molar sodium lactate-Ringer's solution. Subsequently the sulfonamide was given orally with 3 grams of sodium bicarbonate for each gram of sulfonamide.

It has been reported[15,28] that in certain mixed infections, when some organisms are resistant to treatment, the "modus operandi" of antibiotic

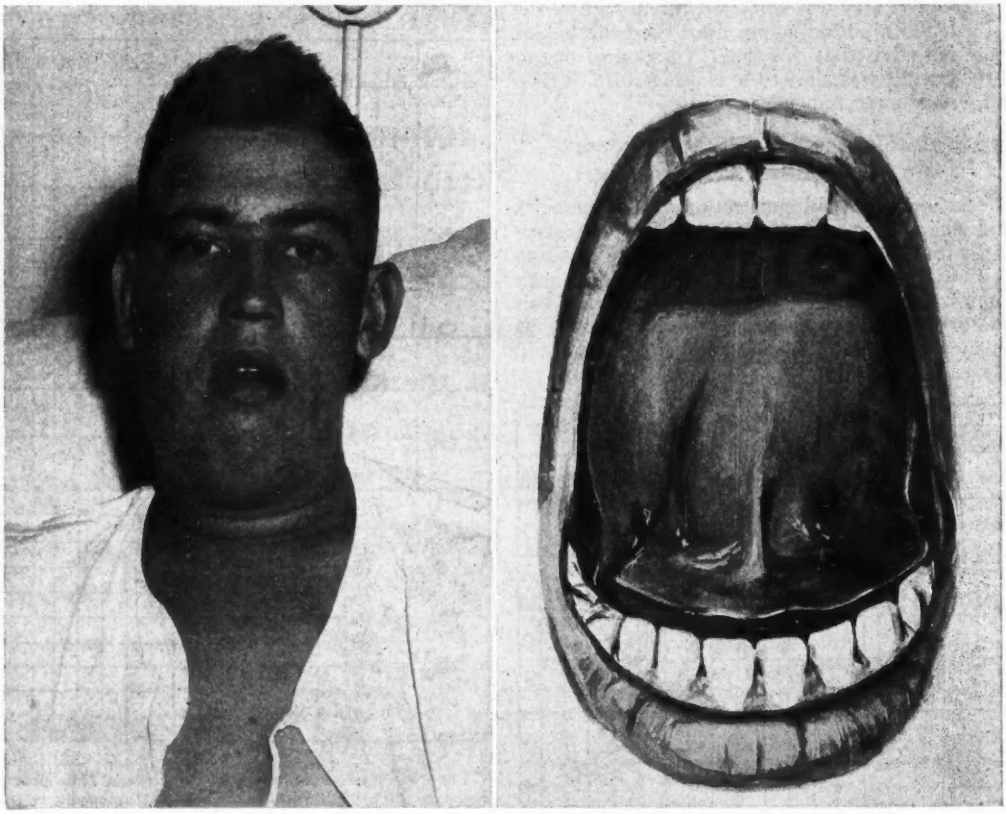


Fig. 4.—Case R.A.P. Severe case of Ludwig's angina. (A) Photo showing swelling of neck structures still present forty-eight hours after beginning treatment. (B) Drawing of cauliflower mass beneath tongue which was found to be a diagnostic feature in all cases of Ludwig's angina.

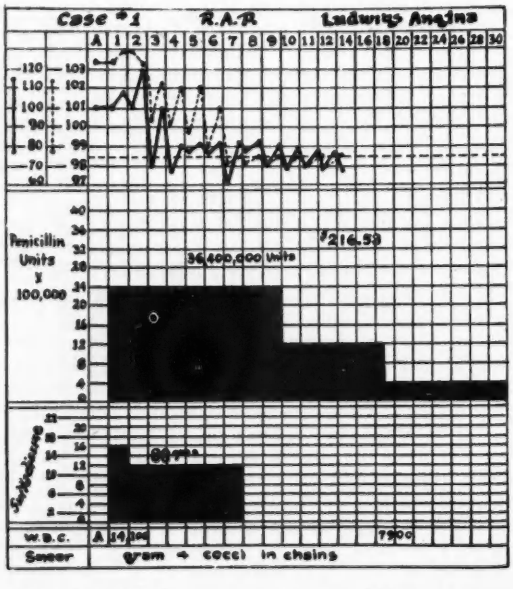

Case #1 R.A.P. Ludwig's Angina
A 1 2 3 4 5 6 7 8 9 10 11 12 14 16 18 20 22 24 26 28 30
Penicillin Units x 100,000
216.53
36,400,000 units
Sulfadiazine
60 gms.
W.B.C.
A 24 hrs
7900
Smear
gram + cocci in chains

Fig. 5.—Clinical summary of case R.A.P. showing course of illness with "balanced therapy" in massive doses.

therapy is to suppress the sensitive group while the natural immunity of the host removes the others. Perhaps this explains the necessity for prolonged treatment in many cases of throat infection and the tendency for them to relapse when the course of treatment is too short.

The authors have noted cases which have developed the socalled hepato-renal syndrome following the administration of as little as one gram of a sulfonamide to a dehydrated patient with a severe throat infection. Three cases of dermatitis, two of which were exfoliative in type, have been treated because of sulfonamide sensitivity. The first dose of the sulfonamide, when given to a case of severe fulminating throat infection should be administered diluted in a suitable alkaline intravenous infusion.

As a result of mass sulfonamide prophylaxis undertaken by the military services against respiratory infections and rheumatic fever it was found that the incidence and morbidity of these diseases was not materially decreased. However, a small percentage of these prophylactically treated individuals became sensitive to sulfonamide drugs.

It had become a common practice before the advent of penicillin to use the sulfonamides as

a specific and even a prophylactic in any and all types of throat infections. We do not advocate this. The purpose of this paper is to call attention to a safer and better method of treating this type of case. It is illogical to risk sensitizing an individual for the treatment of a tonsillitis or pharyngitis which could be treated more efficiently with pencillin rather than with a sulfonamide. Penicillin treated cases do not need frequent blood counts and microscopic urinalysis, which are necessary for management of cases receiving sulfonamides. The use of penicillin in the treatment of throat infection is indicated[18,24] because alpha and beta hemolytic streptococci, which are often sulfa-resistant, are the most frequent cause of throat infections.[6] In this series of 561 cases all alpha and beta types were favorably affected by penicillin. This was evidenced by fewer hospital days, lessening of discomfort, and shortening of the contagious phase of the illness.

ORAL ADMINISTRATION OF PENICILLIN

The oral administration of penicillin has been proved adequate by producing satisfactory therapeutic blood levels and excellent clinical results. Collen[7] reports 12 cases of pneumococcic pneumonia which were treated with oral penicillin administered in dosage of 200,000 units initially followed by 100,000 units every two or three hours. Two grams of calcium carbonate were given with the penicillin. Therapeutic blood levels were established and maintained on this regime and results were wholly satisfactory. Libby[13] used a gelatin capsule containing 150 to 300 units per mg. of sodium and calcium salts of penicillin suspended in cottonseed oil. This gave therapeutic blood levels of .03 to .06 units per cc. Burke and his associates[5] state that the penicillin must be protected from the destructive power of hydrochloric acid of the stomach and yet must be released and subsequently absorbed before it reaches the inhibitory influence of the Escherichia coli bacilli. He advocates administering two aluminum hydroxide tablets 30 minutes before one gelatin capsule (treated with 1-20 formaldehyde for five seconds and 70 per cent alcohol for five minutes), containing 100 units of penicillin. He obtained a rapid initial rise within the first half hour, with a therapeutic level still present four to five hours later. It was concluded that when the oral dose was two times or more greater than the parenteral dose, blood levels exceeded the parenteral medication blood levels. Welsh[27] reports that penicillin blood levels may be prolonged by using aluminum hydroxide as a vehicle.

Keith and others[2,10,12,14,20] report the successful treatment of throat infections by penicillin orally. Various methods produced and maintained effective blood levels such as penicillin mixed with egg, or other foods, taken concurrently with aluminum hydroxide or taken alone dissolved in tap water. It was generally concluded that the drug should be protected from inactivation by gastric acidity. One hundred thousand units every three hours provided therapeutic blood levels within or above the effective anti-bacterial range of most susceptible organisms. Woodward and Holt[28] report the treatment of pharyngitis and nasopharyngitis by the topical application of penicillin. These topical applications consisted of sprays of 500 units per cc. of isotonic salt solution combined with lozenges (800 units per lozenge), lozenges alone, or spray alone. It was concluded that the action of penicillin was more bacteriostatic than bactericidal, that the topical application was beneficial and that lozenges were the best vehicle. In our own experience it was concluded that ice cream constitutes the best vehicle.

CLINICAL EXPERIENCE WITH THE ORAL ADMINISTRATION OF PENICILLIN IN ICE CREAM

The use of ice cream as a vehicle for penicillin administration is not original with the authors of this paper. We believe that ice cream was first used as a vehicle by Comdr. R. N. Nolan (MC), U.S.N. (Ret.) at the United States Naval Training Center, San Diego, California. In this paper we have attempted to apply Comdr. Nolan's formula, with slight variation, to the treatment of various types of acute infectious diseases and throat infections. We have, furthermore, attempted to determine growth inhibition blood levels obtained on test organisms. Our study is by no means complete; nevertheless, we have discovered a useful therapeutic weapon and are accumulating evidence that virulent infections can be removed from or inhibited in the oropharynx.

Ice cream as a vehicle serves several purposes. It is easy to mix. It partially disguises the peculiar taste of penicillin and the mixture is palatable. The mixture is a demulcent and is held in a tenacious film in the oral pharynx for a considerable period of time. Ice cream acts as an anacid. Because of its low temperature the penicillin remains stable.

The vehicle is readily obtainable, the recipe* is easy to compound and the total cost is further reduced. Chocolate flavored ice cream covered the bitter taste of the penicillin most effectively.

In the series of cases reported, the penicillin ice cream was prepared fresh daily. The stock of penicillin used in the mixture was kept in the pharmacy at ice box temperature. The mixture was made in the morning and placed in an ice cube tray in an ordinary icebox and became frozen in approximately six hours. Each cube represented one dose and an ample supply was maintained at all times. The mixture, if kept frozen, can be kept as long as any ice cream preparation.

Cases treated with penicillin ice cream were instructed to hold the preparation in the oral

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* The recipe is as follows: by an electric malt mixer mix one quart of ice cream with one million units of penicillin crystals, previously dissolved in 50 cc. of cold tap water. Thoroughly mix and pour into an ordinary ice cube tray and allow to freeze until solid. By means of a ruler divide the tray into 40 equal cubes. Each cube then of approximately 25 cc. contains 25,000 units of penicillin. Special trays may be adapted for individual ice boxes. Such adaptations are ideal for home use. An example of this with special cutter is illustrated (Figure 6).

pharynx as long as possible and to refrain from taking anything by mouth for at least two hours. This served to keep the penicillin at local lesions as long as possible and also prevented high fluid intake which would further reduce the penicillin blood levels. Dehydration in the toxic cases was not extreme; some required fluids which were given during the hour preceding the medication or intravenously. The dosage was one cube (25,000 units) of the mixture every three hours night and day. The hours of administration were arranged so that they did not conflict with meal time.[4]

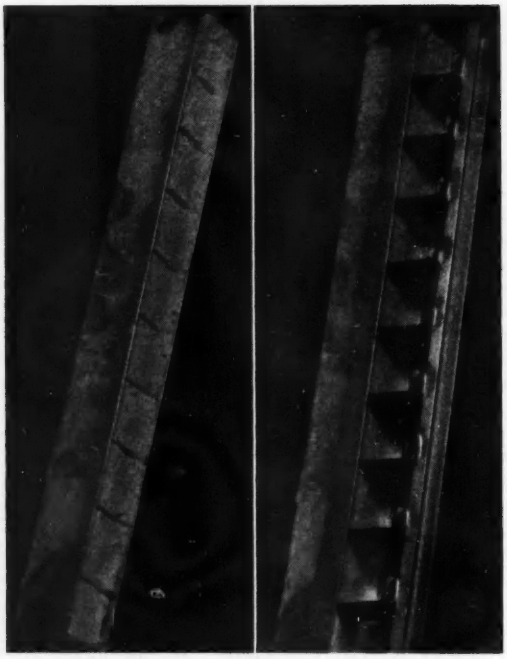

Fig. 6.—Illustration of dispensing tray and view with cutter in place. It is ten cubes long and is ideal for the daily needs of a single case.

The clinical response to this therapy was excellent. Within 12 hours, deglutition was appreciably easier, and after 24 hours fluids and soft diets could be tolerated comfortably. A corresponding decrease was noted in lymphoid tissue edema and mucosal inflammation. Exudative follicles on the tonsils showed regression but not complete resolution. The temperature receded one or two degrees or returned to normal. After 48 hours the patients rarely had difficulty in deglutition and were usually asymptomatic. The mucosa rapidly returned to normal color and the exudative follicles of the tonsils or pharynx disappeared. Some pus might be expressed from the deep crypts of the tonsils at this period (48 hours). Those patients demonstrating cervical adenopathy seldom complained of pain or tenderness on palpation of the nodes. After 72 hours the patients were asymptomatic.

The clinical response has been consistent in the treatment of certain types of cases; pharyngitis, tonsillitis and scarlet fever. The treatment was specific against the spirochetes of Vincent's Angina.[11,17,19,25,26] All of the Vincent's cases treated were of the severe, necrotic, ulcerative type. Results were dramatic and conformed favorably with the results in other spirochetal diseases. Smears rapidly became negative and progressive healing began immediately after treatment was started.

One case illustrates that resistance is often only relative to the size of the dose of penicillin. This is particularly demonstrated by one case in our series. A patient with scarlet fever showed marked improvement after 48 hours on oral penicillin, when suddenly his throat became acutely inflamed and large shallow ulcers appeared on both tonsils, covered with a dirty exudative membrane. Concurrent with this development his rash became more intense. To demonstrate that his resistance was only relative he became normal within 48 hours after vigorous treatment with 100,000 units of penicillin hourly for 48 doses administered intramuscularly.

By this mode of administration (penicillin ice cream) one may expect a local effect on the pathogenic bacteria harbored in the oral and pharyngeal mucosa. In addition there is the systemic effect from that absorbed into the blood stream. It is likely that future experimental studies may reveal an equal efficiency and economy compared to intramuscular penicillin, if the dose, interval of administration, and vehicles for various types of cases are once determined.

Because the potency of penicillin is maintained longer under low temperatures, a frozen vehicle, such as ice cream, lends itself well to hospital service. Penicillin ice cream is easily stored in an ice box and can be administered without further preparation.

TREATMENT OF SCARLET FEVER BY PENICILLIN IN ICE CREAM

(Observation of 150 Cases)

Previously the routine treatment of scarlet fever consisted of scarlet fever streptococcic antitoxin in a dose of 18,000 U.S.P.H. units for adults. This was given intramuscularly in two doses, on admission, after careful evaluation of any allergic diathesis.

In most principles our observations concur with those presented by Ashley.[1] With the availability of penicillin, cases were given either antitoxin, oral penicillin or both. Complications were few and recovery was more rapid in those receiving both agents. Desquamation began within 18 to 36 hours. The erythema faded in 36 hours. The residual red throat and soreness persisting after antitoxin disappeared under the influence of oral penicillin. The average case was clinically well in 48 hours or less. Many cases did not desquamate when given this combined treatment. Sulfonamides have been abandoned by us in the treatment of scarlet fever because the streptococci causing scarlet fever were found to be resistant to them.

A recent survey[21] (254 throat cultures showed a beta hemolytic streptococcus carrier rate of 22.5

per cent). These studies were made on a representative group of the personnel at a large military training center in Southern California.

Two hundred and nine cases of scarlet fever were treated with 1,000,000 units of penicillin, given orally, in a period of seven days and uniformly responded with negative throat cultures for beta hemolytic streptococci. Only 158 cases, or 75 per cent, remained culture negative at the end of one week.[22] This figure is inconclusively elevated above the carrier rate of 22.5 per cent at the same activity. An additional 15 per cent of part of the series became positive during the second week after treatment ceased. The preventive value of this method of treatment, epidemiologically, can be readily seen.

Breese[3] reports that a moderate dose of penicillin for a period of eight days reduced complications of scarlet fever to 8 per cent. Our own therapeutic program reduced complications below their figure.

We observed one fatal case of homologous serum jaundice presumably from human scarlet fever convalescent serum. About 2 per cent of the series of scarlet fever cases were complicated by rheumatic fever. A few developed otitis media.

In conclusion, for the treatment of scarlet fever we advocate the use of scarlet fever streptococcus antitoxin, 18,000 U.S.P.H. units (or 50 cc. of human convalescent serum, if available) and oral penicillin ice cream, 25,000 units every three hours for five to seven days.

PENICILLIN BLOOD LEVELS

We have made a total of 184 penicillin blood level determinations. Of this total, 138 were done on patients receiving penicillin ice cream (25,000 units) every three hours; and 46 on patients receiving penicillin intramuscularly, average dose of 45,000 units every three hours. The highest initial levels were obtained by the parenteral administration with the average reading showing 0.165 units per cc. This is compared with an average penicillin blood level of orally administered penicillin of 0.053 units per cc. (Figure 7.) However, when administered parenterally, there was marked decrease in the blood level of penicillin to an average of 0.093 units at two hours, while following oral medications there was an initial rise up to 0.070 units per cc. at one and one-half hours followed by a level of 0.053 at a two-hour period. It is conjectured that had the oral dose been as high (45,000 units) there would perhaps have been a corresponding increase in the penicillin blood level.

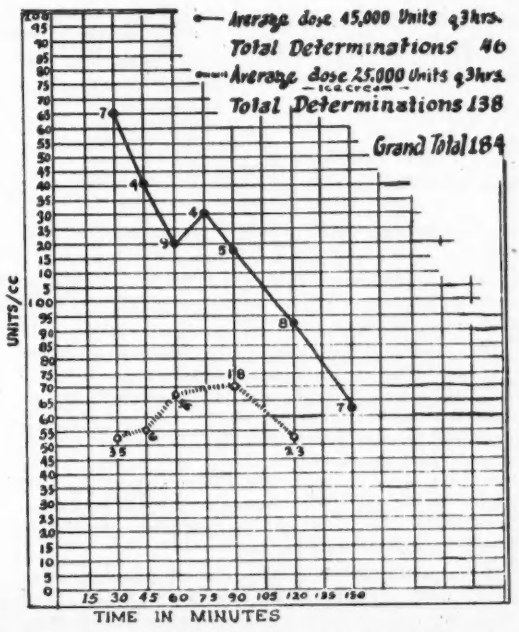
Average dose 45,000 Units q3hrs.
Total Determinations 46
Average dose 25,000 Units q3hrs.
— Ice cream —
Total Determinations 138
Grand Total 184
UNITS/CC
TIME IN MINUTES
15 30 45 60 75 90 105 120 135 150

Fig. 7.—Graph showing results of blood level determinations of penicillin. Solid line indicates intramuscular administration, broken line, oral administration.

SUMMARY

1. The therapeutic measures used in the treatment of 561 cases of acute infections of the throat have been discussed.

2. Penicillin ice cream, 25,000 units every three hours has been offered as a therapeutic measure for the treatment of acute tonsillitis, pharyngitis, scarlet fever throats and Vincent's infections of the throat and mouth. This method of administration may be used for other infections caused by organisms susceptible to penicillin.

3. Streptococcus antitoxin serum 18,000 U.S.P.H. units followed by penicillin ice cream, 25,000 units every three hours for five to seven days has been recommended as the treatment of choice for scarlet fever.

4. Massive parenteral doses of penicillin without surgical interference is preferred for proper management of peri-tonsillar abscess unless spontaneous drainage is imminent.

5. The absolute need for prolonged therapy to prevent the tendency to relapse is discussed for cases of peri-tonsillar abscess and other conditions.

6. Balanced chemotherapy with penicillin parenterally and sulfonamides intravenously (later orally) is recommended for certain overwhelming and fulminating infectious diseases, including those of the throat.

7. Penicillin blood levels obtained by the inhibition of test organisms using the serial dilution method have been presented. Therapeutic blood levels were obtained and sustained for over two hours with penicillin ice cream. The levels were not as high as those with parenteral administration but were therapeutically satisfactory in the cases studied by us.

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STUDIES SHOW NEW DRUG SUPPRESSES MILD FORM OF MALARIA

A new antimalarial drug, pentaquine (SN 13 276—a complex chemical with the appearance of yellow needles), has been found effective in suppressing infections due to the commonest and mildest form of the disease known as Plasmodium vivax, according to the October 12 issue of *The Journal of the American Medical Association.*

R. F. Loeb, M.D., New York, chairman of the Board for Coordination of Malarial Studies, in cooperation with other members of the board, investigated the action of the drug in civilian establishments under the sponsorship of the Committee on Medical Research of the Office of Scientific Research and Development and in various Army installations.

Some of the pertinent conclusions drawn from these studies are:

Pentaquine, studied in mice, rats, dogs, monkeys and human beings, is rapidly and completely absorbed from the gastrointestinal tract.

It has an undesirable, but, at present, ill defined effect on the heart and circulation when administered in large doses.

The poisonous quality of pentaquine is too great to warrant its use in preventive treatment or prolonged suppression of malaria.

The action of this drug was studied on 171 white volunteers. The investigators concluded that a daily dose of 60 milligrams of pentaquine and two grams of quinine administered concurrently in divided doses every four hours for 14 days is "sufficient to produce radical cure of severe infections due to Plasmodium vivax." However, they caution that the daily dose of 60 milligrams should not be exceeded. "Pentaquine should be administered only under close medical supervision, preferably during hospitalization," they add.

In conclusion the article states that the poisonous effect of the drug in Negroes and persons of mixed racial extraction and the safe treatment dosage for children are at present undetermined.

Trends in The Age Distribution of Childhood Diseases*

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THE acute communicable infections commonly referred to as the childhood diseases may be readily divided into groups: (1) Those which every individual must expect to have at some time during his life—pertussis, measles, chickenpox, German measles, mumps; (2) those which he may acquire but for which specific artificial immunity is available—diphtheria and smallpox; and (3) those which he may acquire but for which there is no specific protection—poliomyelitis. Scarlet fever should also be placed in this last group if you agree that immunization for this disease is not specific.

Upon first exposure, most individuals are highly susceptible to all diseases of the first group and to those of the second unless previously immunized. Infection is acquired with the first suitable exposure, normally occurs early in life and, in most cases, results in a lasting immunity. The designation of "childhood diseases" naturally follows. That these infections are not necessarily childhood diseases is substantiated by the occasional case in adult members of the population and the epidemics that have occurred in the armed forces. Such persons have not had suitable exposure during childhood or have lost their specific protection.

The control of the acute communicable diseases specifies certain efforts to prevent the spread of these infections. The success of such control measures may be judged by the incidence of the various diseases over a long period of time. Many of them appear as sharply defined epidemics, and the successive peaks of these epidemics closely follow the population trends, especially the changes in the number of children. In general, the diseases of the first group above have not been successfully controlled by public health agencies: the epidemics progress until the supply of available susceptibles has been exhausted. Intensive efforts have been directed toward the protection of children from these infections: during infancy we would delay the attack until childhood, and during the school years we would further postpone infection in order to improve the average daily attendance. Such efforts, if successful, would result in an increased incidence of these childhood diseases in older children and adults even when there is no reduction in the total number of cases. Disregarding, for the moment, the merits of controlling the childhood diseases, the data at hand may be studied to determine the success of present measures. Has there been a shift in the age distribution of these diseases from the younger to an older age group?

The reported cases of the various childhood diseases in San Joaquin County during the years 1925-1944 have been analyzed for age distribution. While the population group and the number of cases are not large the figures for this county may be considered of value for other reasons. The entire county including rural and urban areas is served by the San Joaquin Local Health District. The District has had a consistent administrative policy during the 20-year period. Since 1925 there has been a 50 per cent increase in field nursing service, a factor which should maintain or improve communicable disease control. Records have been consistently and carefully kept and, no doubt, reporting has improved during this time.

The general data used in this analysis is presented in Table I. Five-year periods have been used to increase the significance of the figures and to avoid the wide fluctuations between epidemic and non-epidemic years. The data show an increase in the total number of cases of measles, mumps, and chickenpox; a downward trend in scarlet fever, diphtheria, and smallpox; a recent reduction in pertussis; and a slight increase in German measles. The 200 cases of poliomyelitis are about equally divided between the four five-year periods. There has been no case of smallpox since 1939. In recapitulation, attention is called to the total number of cases in younger children. Before they reach the age of ten years, children have had 91 per cent of the reported whooping cough, 84 pr cent of the chickenpox, 80 per cent of the measles, 62 per cent of the scarlet fever, 55 per cent of the mumps, 50 per cent of the German measles, 50 per cent of the diphtheria, and 49 per cent of the poliomyelitis. Only smallpox has had a high incidence in adults.

Present interest is directed toward the trends in age distribution, and this can be shown only by taking each disease separately. Starting with chickenpox as the most mild infection, but highly contagious, the graph (Chart I) shows a steady increase in the incidence in preschool children throughout the 20-year period with a corresponding decrease in children of school age. Measles (Chart II), pertussis (Chart III), and scarlet fever (Chart IV) also show an increase in preschool children but not so marked or so regular as that for chickenpox. In contrast, mumps (Chart V) and rubella (Chart VI) show an increase in those individuals over ten years of age. Diphtheria (Chart VII) shows a definite shift away from the two younger age groups; the increase in total cases and in children under five during the last five years is cause for concern. Smallpox (Chart VIII) also shows a shift to the older age groups. The figures for poliomyelitis

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are small but, in general, show a shift to the older groups (Chart IX).

The proper evaluation of these findings requires consideration of changes in the total population by age groups. Specific attack rates would be of value for those diseases that show a definite shift. However, the population at various age levels can be only estimated. Children under five years were enumerated by the census as 7,196 in 1930 and 8,729 in 1940. Extensive migration has reduced the value of these figures, and the actual number of births reported in the area may be a better guide for the trends of diseases in this age group. These figures are presented for the various diseases in Table II.

This table indicates that the number of cases of chickenpox in children under one year of age follows very closely the number of births, especially in the last decade. As judged by the number of births and the census figures there has been an increased incidence of chickenpox in children age one through four. Whooping cough in the last ten years has not kept pace with the increasing birth rate: local pediatricians believe this can be explained by the use of pertussis vaccine. Diphtheria has been eliminated in children under one year of age but continues to appear in those age one through four.

In the absence of better data the cases of measles and mumps have been compared with the school population during this period. These figures are presented in Table III. The marked increase in high school attendance in confirmed by the census figures for the age group 15-19:

TABLE 1.—*Percentage Distribution of Reported Communicable Diseases in San Joaquin County by Age*

DISEASE	Age Group	1925-1929	1930-1934	1935-1939	1940-1944	Total 20 Years
CHICKENPOX:	No. of Cases	2,869	3,620	4,694	5,278	16,461
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	20.2	23.4	24.3	28.7	24.8
	5 - 9	62.5	60.6	60.5	56.0	59.4
	10 - 14	12.2	11.9	11.2	11.0	11.5
	15 - 19	1.5	1.6	1.7	1.7	1.6
	20 or over	3.4	2.5	2.3	2.5	2.6
MEASLES:	No. of Cases	3,240	5,736	6,030	7,331	22,337
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	22.5	22.1	23.0	25.3	23.5
	5 - 9	63.4	59.0	56.5	53.3	57.0
	10 - 14	10.5	15.0	16.2	15.3	14.8
	15 - 19	1.7	2.2	3.3	3.3	2.7
	20 or over	1.8	1.4	0.8	3.2	2.0
WHOOPING COUGH:	No. of Cases	1,999	3,213	3,205	2,986	11,403
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	40.9	40.5	41.8	47.7	42.8
	5 - 9	51.4	50.9	48.4	45.0	48.8
	10 - 14	6.2	6.3	7.8	5.4	6.6
	15 - 19	0.4	0.7	0.7	0.6	0.6
	20 or over	1.6	1.4	1.2	1.3	1.3
MUMPS:	No. of Cases	2,649	2,647	4,034	5,926	15,256
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	13.5	10.2	9.3	10.3	10.5
	5 - 9	48.8	49.8	45.2	42.6	45.7
	10 - 14	26.5	27.1	30.0	27.5	27.9
	15 - 19	3.7	6.4	7.3	9.3	7.3
	20 or over	7.4	6.4	8.3	10.4	8.6
GERMAN MEASLES:	No. of Cases	2,318	263	687	2,960	6,228
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	13.4	19.7	14.7	10.4	12.4
	5 - 9	46.4	49.5	45.4	29.6	38.4
	10 - 14	29.6	23.2	27.1	29.8	29.2
	15 - 19	4.6	2.3	6.3	20.0	12.0
	20 or over	5.9	5.3	6.5	10.5	9.5
SCARLET FEVER:	No. of Cases	1,930	1,134	1,489	1,012	5,565
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	16.7	17.0	18.2	24.6	18.7
	5 - 9	42.8	47.2	42.0	44.6	43.8
	10 - 14	23.8	19.5	21.7	18.3	21.4
	15 - 19	6.6	6.3	6.6	6.1	6.3
	20 or over	10.6	9.8	11.4	6.3	9.9
DIPHTHERIA:	No. of Cases	382	127	129	186	824
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	27.6	26.8	9.3	16.7	22.0
	5 - 9	29.1	31.5	27.1	25.8	28.4
	10 - 14	14.6	10.2	16.3	14.5	14.2
	15 - 19	5.4	6.3	11.6	7.0	6.8
	20 or over	23.8	25.2	35.7	36.0	28.6
POLIOMYELITIS:	No. of Cases	42	54	47	57	200
	All Ages	100.0	100.0	100.0	100.0	100.0
	0 - 4	45.0	16.5	27.6	15.8	25.0
	5 - 9	23.8	29.6	14.9	28.1	24.5
	10 - 14	14.3	35.2	17.0	22.8	23.0
	15 - 19	4.8	7.4	14.9	14.0	10.5
	20 or over	11.9	11.1	25.6	19.3	17.0
SMALLPOX:	No. of Cases	125	80	85	0	290
	All Ages	100.0	100.0	100.0		100.0
	0 - 4	13.6	7.5	5.9		9.7
	5 - 9	16.0	23.8	11.8		16.9
	10 - 14	6.4	12.5	3.5		7.2
	15 - 19	10.4	8.8	18.8		12.4
	20 or over	53.5	47.5	60.0		53.8

8,255 in 1930 and 13,072 in 1940. This increase is still less than the increase in the cases of mumps in children of high school age.

From these figures, accepted for what they may be worth in the light of limited knowledge of population composition, it may be said that certain diseases have not been altered in their attack on children by efforts to protect the child. In other diseases that have changed, a more satisfactory explanation is available: inoculations for diphtheria and smallpox; widely spaced major epidemics of german measles—1928 and 1942;

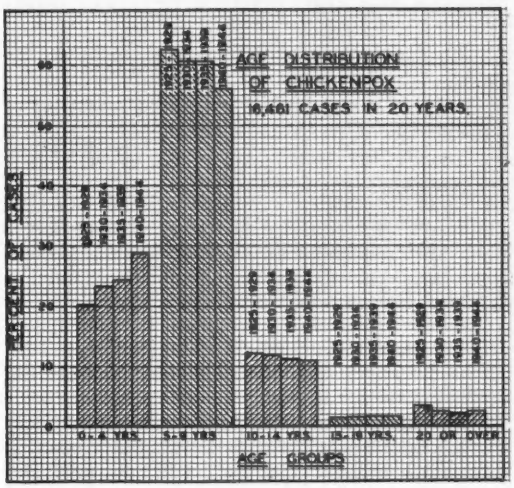

Chart I.

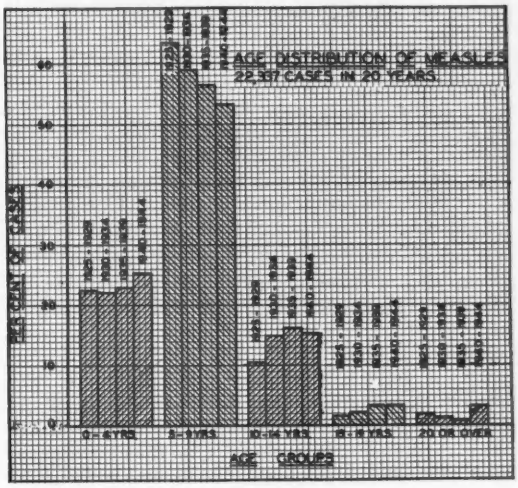

Chart II.

TABLE 2.—*Communicable Diseases in Children Under 5*

	Age Group	1925-1929 Number	1930-1934 Number	1930-1934 Change	1935-1939 Number	1935-1939 Change	1940-1944 Number	1940-1944 Change	Total 20 Years
Average Annual Births		1,635	1,510	− 8%	1,845	+ 22%	2,695	+ 46%	38,436
CHICKENPOX:	—1	73	92	+26%	144	+ 56%	193	+ 34%	502
	1 & 2	199	296	+49%	388	+ 31%	570	+ 47%	1,453
	3 & 4	309	457	+48%	609	+ 33%	753	+ 24%	2,128
	0 — 4	581	845	+45%	1,141	+ 35%	1,516	+ 33%	4,083
PERTUSSIS:	—1	134	218	+62%	231	+ 6%	256	+ 11%	839
	1 & 2	274	439	+60%	476	+ 8%	538	+ 13%	1,727
	3 & 4	410	644	+57%	634	− 2%	628	− 1%	2,316
	0 — 4	818	1,301	+59%	1,341	+ 3%	1,422	+ 6%	4,882
DIPHTHERIA:	—1	12	2	−83%	0	−100%	0	....	14
	1 & 2	49	11	−78%	6	− 45%	11	+ 83%	77
	3 & 4	43	21	−51%	6	− 71%	20	+230%	90
	0 — 4	104	34	−67%	12	− 65%	31	+160%	181
SMALLPOX:	—1	2	1	....	0	....	0	....	3
	1 & 2	5	1	....	3	....	0	....	9
	3 & 4	10	4	....	2	....	0	....	16
	0 — 4	17	6	−65%	5	− 17%	0	−100%	28
MEASLES:	—1	70	91	+30%	96	+ 5%	163	+ 70%	420
	1 & 2	264	467	+77%	443	− 5%	733	+ 65%	1,907
	3 & 4	396	712	+80%	853	+ 20%	961	+ 13%	2,922
	0 — 4	730	1,270	+74%	1,392	+ 10%	1,847	+ 33%	5,239
SCARLET FEVER:	—1	13	3	−77%	18	+500%	6	− 67%	40
	1 & 2	83	65	−22%	74	+ 14%	83	+ 12%	305
	3 & 4	227	125	−45%	179	+ 43%	160	− 11%	691
	0 — 4	323	193	−40%	271	+ 40%	249	− 8%	1,036
MUMPS:	—1	17	5	−71%	12	+140%	17	+ 42%	51
	1 & 2	69	87	+26%	112	+ 29%	188	+ 68%	456
	3 & 4	273	179	−34%	246	+ 37%	406	+ 65%	1,104
	0 — 4	359	271	−24%	370	+ 37%	611	+ 68%	1,611

TABLE 3.—*Number of Cases in School Children*

	1925-1929 Number	1930-1934 Number	1930-1934 Change	1935-1939 Number	1935-1939 Change	1940-1944 Number	1940-1944 Change
Elementary Schools, A.D.A.	13,500	14,170	+ 5%	13,620	− 4%	14,830	+ 9%
Measles, Age 5-14	2,395	4,256	+78%	4,389	+ 3%	5,023	+14%
High Schools, A.D.A.	3,535	4,790	+35%	6,710	+40%	6,956	+ 4%
Mumps, Age 15-19	98	169	+73%	295	+75%	551	+87%

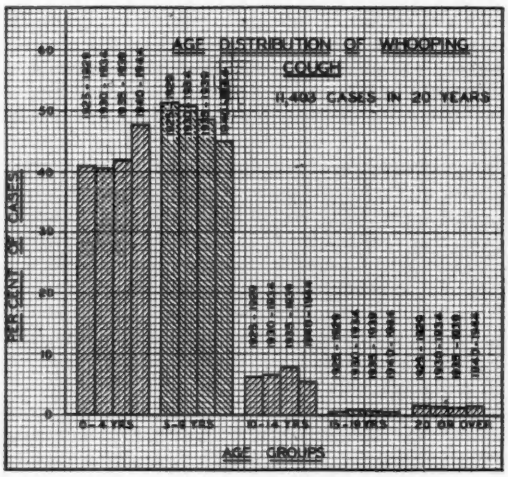

Chart III.

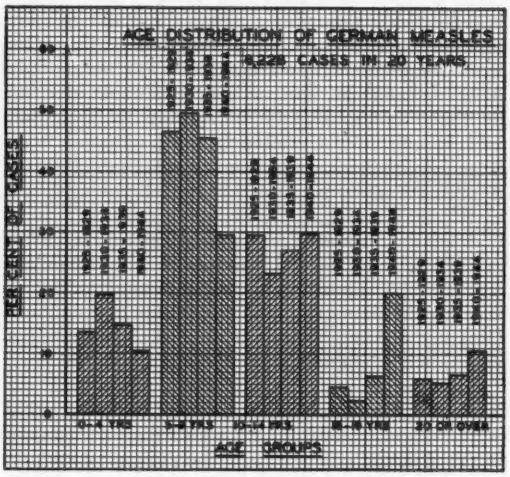

Chart VI.

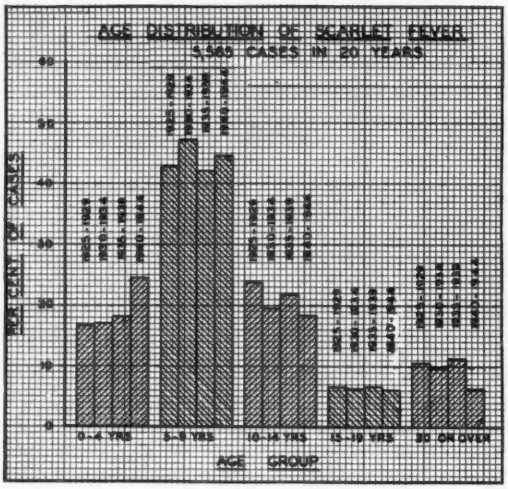

Chart IV.

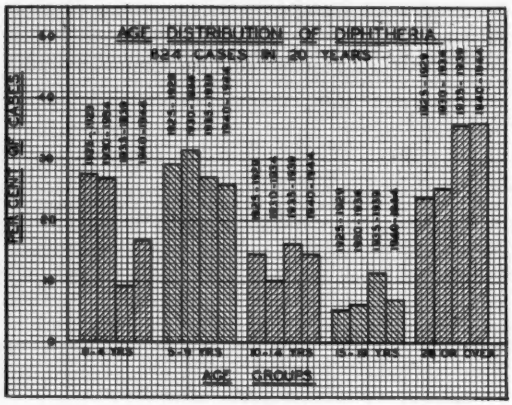

Chart VII.

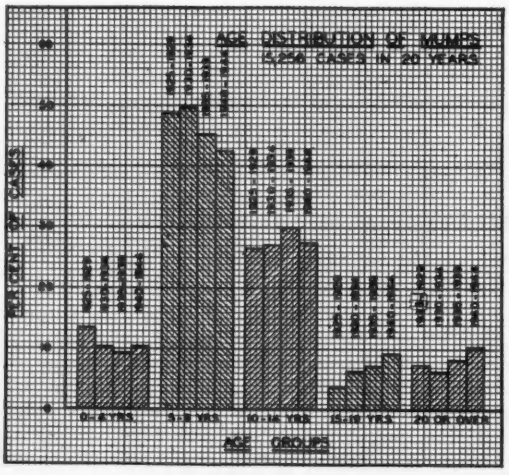

Chart V.

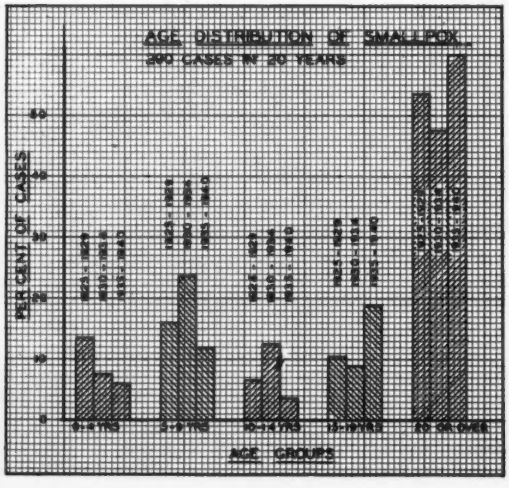

Chart VIII.

immigration in the group in which mumps increased. Several explanations may account for the shift in pertussis and the reduction in total cases in the last five years: successful immunization; modified attacks which were not recognized; or reluctance to admit failure of immunization by making a specific diagnosis. Scarlet fever, no longer a specific entity, shows slight actual change in age distribution, but there has been a reduction in the total number of cases. It cannot be claimed that isolation and quarantine have been responsible for the shift seen in poliomyelitis.

Turning again to those diseases which everyone must expect to have, much time is spent in trying to prevent infection until adult years are reached. Is this a rational objective? Adults with chickenpox, measles, or pertussis are frequently more seriously ill than are children with these infections; there are specific complications which may accompany mumps; and rubella has now been shown to be an unfortunate disease to have develop during early pregnancy. From the data available, it would appear that much of the effort has been wasted; regulations and isolation of cases and contacts have not controlled the spread of measles, mumps, chickenpox, german measles, and pertussis as judged by the number of cases and age distribution. If it is claimed that a number of people escape these infections throughout their lives as a result of these efforts, then it should be admitted that this number is no greater in San Joaquin County today than it was 20 years ago.

If present efforts have not curtailed certain diseases, should the procedure in regard to them be modified? The Health Department may have educated the public and the schools to believe that these diseases are controlled and would "lose face" in admitting failure. But it appears that factors such as the number of susceptibles in the community and their habits and environment—housing, crowding, migration—have greater influence on the spread of certain diseases than can be offset by isolation of cases and supervision of contacts.

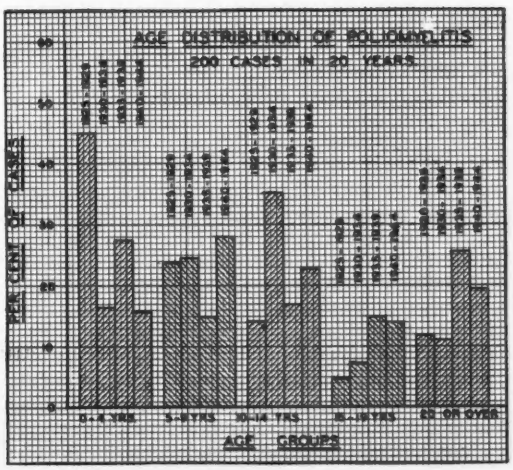

Chart IX.

If childhood is the most desirable period in which to have certain diseases can epidemics be sponsored? The schools would clamor unless they first reviewed the cases that now occur in school. While a reported sponsored epidemic (Levine's experiment with mumps) ended somewhat disastrously one may speculate on what might happen should the same course be followed for several generations. Had the parents and teacher who contracted mumps been deliberately and repeatedly exposed during childhood by similar epidemics, they would not have remained as susceptibles at the time of this experiment. His suggestion that more complications develop in cases of the third and fourth generation does not necessarily hold. Every epidemic, "controlled" or not, runs through several generations of cases. While the Health Department may not sponsor epidemics, efforts can be diverted to more profitable fields where there is promise of dividends.

SUMMARY

1. Certain of the childhood diseases have shown a change in age distribution during the years 1925-1944 in San Joaquin County. Such changes may result from:

(a) Increased protection or increased exposure of certain age groups.

(b) A change in the number of susceptibles within an age group by an increasing birth rate or migration of popuation.

(c) Improved reporting of cases within a specific age group.

2. For those diseases which have shown an increase in the total number of cases, protection of children does not appear to be a factor in changing the age distribution.

3. If efforts to protect the child from the common virus diseases of childhood are ineffectual, they should be modified with prevention of complications and mortality as an objective.

4. Let us see that the infant is immunized against pertussis, diphtheria, and smallpox; see that the young child has modified measles; let chickenpox come when it will; hope that mumps comes before puberty and German measles any time before pregnancy; prolong the protection against smallpox and diphtheria as long as possible.

Discussion by H. O. SWARTOUT*, M.D., Dr. P.H.

While the time available after being invited to discuss Dr. Bingham's paper was not sufficient to permit collection and analysis of comparable data for Los Angeles County, there are certain general observations that can be made. I believe the shifts in age-groups most commonly attacked in Los Angeles County by the "childhood diseases" mentioned in his paper have been quite similar to those in San Joaquin County. Recently, however, an additional important factor has tended to check the trend toward a lower average age for the incidence of some of these diseases. We have had a very large influx of working men and their families from out of the state.

* Los Angeles County Health Officer.

many of these people coming from areas either much less densely populated than ours or not carrying on as good immunization programs as ours, or both. The result has been to add many susceptibles of all ages to our population, not simply infant and small children susceptibles.

For several years before becoming Health Officer, I kept collecting figures with a bearing on what might be termed the relative inevitability or likelihood that a person would develop certain diseases some time in life. By questioning audiences of adults — sometimes combined audiences of adults and older children — I found that the following percentages of these people *remembered* having had the following diseases, or having been told by their parents that they had had them: Measles, 96 per cent; chickenpox, 95 per cent; whooping cough, 74 per cent; mumps, 46 per cent; scarlet fever, 27 per cent.

I can agree with Dr. Bingham that what we have done to prevent the spread of such diseases as measles, chicken pox, mumps, German measles, and even scarlet fever does not seem to have accomplished much. I also agree that we should put more emphasis on means of preventing complications and lowering mortality. That under present circumstances we can "see that the young child has modified measles" in all or even in a large proportion of cases, I doubt. There are too many cases in which the *fact* of exposure is unknown until the disease develops, and too many more in which the time of first exposure is not known. Modification of measles is, of course, a good idea and should be put into practice wherever the circumstances warrant.

Scientifically speaking, even though it may seem like a throwback to the days when people said, "I want Johnny to have the measles and get it over with," I see much in favor of sponsored and controlled epidemics of some of the contagious diseases that we do not know how to prevent. I believe that you can imagine, however, what would happen to the health officer who sponsored such an epidemic, if any fatalities occurred in its course.

METHANOL POISONING *

EMIL BOGEN, M.D., *Olive View, California*

METHANOL poisoning is an important cause of disability and death in the military services. Instances have occurred in more than half a dozen different places in the Pacific area alone during the past year or so. At one station alone, methanol poisoning was observed six different times. In all, 30 persons were involved, five of whom died.

Methanol poisoning is by no means confined to the military services. Thousands of civilian cases have been reported. However, the restrictions against the use of alcohol by enlisted men in the Navy, the obstacles to successful bootlegging of potable alcoholic beverages while afloat, the general availability of methanol in many places, and the reckless avidity for intoxication notoriously exhibited by some naval personnel, all make the danger more imminent among their ranks.

Methanol poisoning may occur accidentally through inhalation of the fumes during industrial processes, or it may result from deliberate attempts at homicide or suicide. Most instances, however, are the result of taking methyl alcohol instead of ethyl alcohol in drinks. Sometimes the user sees the name and poison label, but refuses to heed it, believing it may have been placed there merely to protect beverage alcohol from thieves. Or he may think that the poisonous effect will be inconsequential in a man of his resistance or in the dilution and amounts which he intends to use. More often the poisonous nature of the liquid labeled "Methanol," "Methyl Alcohol," or "Wood Alcohol" without a poison label is not appreciated, or its presence is not recognized in a container labeled "Columbian spirits," "Wood spirits," "Methyl hydrate," "Ditto fluid," "Denatured alcohol," "Lighter fluid," "Refrigerator leak detector," "Alcohol for Halide Leak Detector," "Paint thinner," "Antifreeze compound," or in unlabeled containers, or mixed drinks.

Although the consumption of such liquids may be in attempted violation of the Navy orders against the drinking of intoxicating liquors by enlisted men, or may represent misappropriation of property belonging to the United States Government, none but a fanatic would hold that such an offense should be punished by the blindness or death that so often result from this form of poisoning. Accordingly, every effort should be made to prevent such catastrophes and to ameliorate their consequences if they do happen.

Opinions differ as to how containers should be labeled for greatest safety. On the one hand is the argument that the labels "wood alcohol," "methyl alcohol" and "denatured alcohol" are more likely to attract the unwary seeker for beverage alcohol than to warn him of the poisonous liquid of which he may have heard. On the other is the opinion that the contents of containers labeled "methanol," "denatured ethanol," "lighter fluid," etc., are likely to be taken because of their odor and appearance, with the imbiber ignorant of their real composition. There is general agreement, however, that every such container should bear a large and conspicuous poison label. This has been provided for in many laws, orders, regulations and agreements, etc. Thus an agreement between the U. S. Public Health Service and the manufacturers of methanol or related products provides that any material containing more than 15 per cent of free methanol shall be labeled "Poison, Contains over . . . per cent Methanol. Cannot be made non-poisonous." However, this requirement was often ignored during the war and mislabeled and even entirely unlabeled containers containing methanol were repeatedly encountered in naval facilities.

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* Read before the Section on Pathology and Bacteriology, at the Seventy-fifth Annual Session of the California Medical Association, Los Angeles, May 7-10, 1946.

Particularly to be deplored was the unqualified label "Alcohol" or "Alcohol for Halide Leak Detector" which was found on containers of methanol. Measures were taken to remove these misleadingly labeled containers, but several lives were lost before this was done.

An educational campaign directed at informing enlisted men of the dangers of death or blindness from drinking methanol has been carried out by some activities, by notices, lectures, and even by posting letters describing the unfortunate plight of one of the men who did lose his sight from drinking such liquor. The fact that further cases and deaths developed later in the same organization as a result of the theft and drinking, by the culprit and his ignorant friends, from a can plainly labeled "Methyl Alcohol" and "Poison" in conspicuous red letters shows that neither labeling nor education may be relied upon to safeguard completely against such tragedies.

Making methanol inaccessible to the men by eliminating it from naval stores may be feasible in some places, where it may be replaced by other agents, glycerine or ethylene glycol for antifreeze, benzine or petroleum ether for cigarette lighters, turpentine for paint thinner, carbon tetrachloride for cleaning agent, denatured alcohol for fuel, and pyridine, diethyl phthalate, etc., for denaturing alcohol. Where it is essential, in the laboratory as a solvent for Wright's stain, for instance, it is packed in small (one ounce) bottles with the dye powder to be mixed with it, and each bottle is labeled "methyl alcohol-poison." But it is also available in pint bottles, which are more dangerous although similarly labeled.

Although industry did learn to diminish greatly the use of ethyl alcohol during prohibition days, and our entire material medica was almost revolutionized by the avoidance of this substance, it would seem very unfortunate if scientific and technological workers were to be deprived of the very valuable uses of methanol. At the same time, the frequency and seriousness of its misuse demands that some precautions be taken to diminish its occurrence. This may be attempted by limiting the number of places where methanol may be kept, storing it in designated places to which only authorized persons have access, and instituting a strict method of accounting for all methyl alcohol on hand. Even this must be vigilantly supervised, since some of our worst instances have occurred through laxity in the enforcement of just such a system. But on the whole, a system of safeguarding methanol similar to that in use for narcotics might greatly reduce the chances for such catastrophes.

The denaturing of methyl alcohol by adding emetic, nauseating or otherwise distasteful materials, as is done with ethyl alcohol, might be effective, but this might interfere with its use in chemical reactions. Another possible safeguard against tragedy might be to require that substances which must be dissolved in methyl alcohol, or preparations containing it, be made under supervised conditions and sent out complete, rather than as separate ingredients to be mixed later. But it seems probable that methanol poisonings may still only too often occur. It is well, therefore, that the physician become cognizant of the diagnosis and treatment of this condition.

Pure methanol is a colorless liquid with a characteristic odor resembling but differing distinctively from that of ethyl alcohol. Its molecular weight is about three-fourths of that of ethyl alcohol, but the specific gravity of .792 is slightly greater. It solidifies at minus 97.8°C., 15 degrees above the ethyl solidification point and it boils at 64.7°C., 13.7 degrees below the temperature at which ethyl alcohol boils. So ethyl alcohol is a more persistent, if initially somewhat more expensive, agent for antifreeze purposes. Methanol ignites at 470 degrees, nearly a hundred degrees lower than ethyl alcohol, and burns with a hot blue flame, so it is widely used as a fuel in cigarette lighters and small lamps, under the name of Columbian spirits.

The pharmacological effects of methanol may depend partly upon its chemical reducing properties, with the abstraction of oxygen from the tissues where it is being oxidized; partly upon its solubility in fat and nervous tissue, which is not, however, as great as is that of ethyl alcohol; partly on its irritating local action, and partly upon the unexplained "anesthetic effect" which it shares with the other alcohols. Some of the effect, however, has been ascribed to the products of the oxidation of methanol, the irritating action of formaldehyde, the acid production of formic acid, and other metabolites produced within the body. Other ill effects have been ascribed to impurities in the methanol itself, but these are encountered much less in the synthetic than in the natural wood spirits, with no variation in toxicity, so it seems improbable that such impurities are considerable in the ordinary case of methanol poisoning.

Despite the popular impression to the contrary, methanol is really much less toxic than is ethyl alcohol in similar doses, and due to the widespread use of the latter, many more deaths result from ethyl alcohol poisoning. However, the slow elimination of methanol in the organisms makes it accumulate during sustained drinking and remain in the body a much longer time. Hence it results in many more cases of permanent disability, especially of vision. Under the circumstances in which it is taken, moreover, there may be a greater tendency to drink the methyl alcohol in higher concentration and more rapidly than is usually the case with ethyl alcohol beverages, with consequently more occasion for large doses to be taken before the alcoholic stupor itself precludes further drinking.

LABORATORY TESTS

The presence of methanol may be suggested by its odor, its low specific gravity, its inflammability, its volatility, and other physical properties, or by its reducing action, or the formation of formaldehyde and other chemical reactions in

which it takes part. Scores of tests have been described and have been critically evaluated by extensive studies such as those of Gettler and of von Oettingen. The method for detection used in Navy laboratories is based upon the oxidation of the methanol in the presence of some ethanol by potassium permanganate, the removal of excess permanganate by oxalic acid, and the demonstration of the presence of formaldhyde in the solution by the addition of a fuchsin-sulfurous acid mixture. This test may be made quantitative by making up, at the same time a set of standards with known concentrations of methanol.

When it is known that methanol and no other alcohols are present, the amount of methanol may be determined by the same procedure used for determining ethyl alcohol in the blood or urine, etc., with potassium dichromatex reagents. But if ethanol standards are used, it should be remembered that the molecular weights of the two substances differ, so that the actual methanol content is only about three-fourths of that indicated in the ethyl alcohol standard. Where it is not known how much of either is present, the results of the two methods described above, applied simultaneously, may enable calculation of the relative amounts of the two forms of alcohol.

CLINICAL FEATURES

The early symptoms of methanol poisoning are so similar to those of ordinary ethyl alcohol intoxication as to arouse little suspicion of the true nature of the condition, and many cases have suffered, accordingly, from the lack of diagnosis and early treatment. The odor on the breath may not be recognized unless specifically sought for, and may be less marked than that of ethyl alcohol. The dilated pupils, peripheral vasodilatation, with flushed face and injected conjunctiva, lessening of inhibitions and dulling of attention, alterations in form and content of speech and behavior, and muscular incoordination manifested in speech and motor activities, posture, gait, and behavior do not reveal the cause of the intoxication. With deeper methanol narcosis, constricted pupils, facial pallor, depression of pulse and respiration, and finally increasing stupor or coma may develop.

In addition to the general anesthetic or narcotic effects, however, methanol is more likely than ethyl alcohol to induce local irritative and general toxic symptoms, such as nausea, vomiting, epigastric or abdominal pain, headache, vertigo, dizziness, malaise, fatigue, weakness, numbness or pulling pains in the legs. These symptoms may develop early, together with the characteristic visual disturbances, nystagmus, pupillary changes and loss of pupillary reflexes, tenderness or pain in the eyeball, especially on pressure or movement, and difficulty in maintaining accommodation, with general blurring of vision.

More severe states are ushered in by excitement, with hallucinations and maniacal activity, or apathy, stupor and developing coma, which may be associated with increased reflexes, opisthotonus and convulsions, dyspnea which may be severe and associated with intense thirst, cyanosis, a rapid, weak pulse and lowering of blood pressure.

Symptoms may develop slowly or temporarily remit, but are likely to increase suddenly and are characteristically more progressive in nature and much more prolonged than the corresponding stages of ethyl alcohol intoxication. The estimated fatal dose is between 100 and 250 cc, but marked variations in individual susceptibility exist, the fatal level in the blood being approximately the same as for ethyl alcohol, about 5 mg. per cc. Since the drug has cumulative effects, however, death may occur with a lower concentration. Death may come suddenly, soon after the onset of the intoxication, or following several days of coma.

The most commonly dreaded neurological effect is optic neuritis. This is usually bilateral. It may start with dimness of vision and scotomata or blind spots, and may progress slowly or rapidly to complete blindness—within a few days or even later—though some improvement may occur subsequently. Ophthalmoscopic examination may show the retinal vessels congested and dilated, blurring of the edges of the optic disc, or an optic neuritis with the presence of exudate into the retina.

Laboratory findings in acute methanol poisoning are variable, except for the presence of methanol in the tissues and body fluids and excretions. With severe acidosis, lactic and formic acid may be found in the urine. Hemoconcentration, albummuria and even glycosuria, and elevation of blood urea and nonprotein nitrogen also have been reported.

The numerous visceral changes which have been described in reported autopsies were generally absent in the five fatal cases previously mentioned. Our most conspicuous finding in these cases was edema of the meninges and brain tissue, with slight flattening of the cerebral convolutions over the cortex and an apparent diminution of cerebro-spinal fluid. There was no cardiac enlargement, the lungs were crepitant throughout except for two instances with hypostatic congestion, the liver showed edema or congestion, without marked fatty changes, the gastric mucosa was hyperemic but appeared atrophic in only one instance, and the kidneys showed no marked changes. Perhaps the changes reported in the literature reflect the effects of prolonged and repeated drinking of irritating and toxic liquids other than methyl alcohol, as they generally resemble those described in old chronic alcoholics, and would, accordingly, be absent in the physically fit young men who had been kept away from alcoholic liquor for the most part until the chance misuse of methyl alcohol brought them to our notice.

The results of a rather intensive investigation of our cases, in which 30 participants were finally located by persistent questioning (although only nine had come in originally to complain of symptoms) suggests that in many such occasions the subjects who are only lightly or transitorily affected may not be detected. The usual mortality figures of more than 50 per cent are thus exag-

gerated by being based only on the more serious cases. Although our total mortality of less than 20 per cent appears low, it includes a number of men who drank only small amounts of the methanol, and we lost more than half of the men who had actually developed serious symptoms from the liquor.

The amounts of methanol consumed by our patients varied from just a taste which was spit out to more than a pint, or eight ounces of pure methanol. Fatalities occurred only in those who took the larger amounts, and recovery in several instances followed the ingestion of as much as six ounces of methanol. Symptoms included headache, nausea and vomiting, cramps, convulsions, stupor, coma, abdominal pain, numbness in legs, blurred vision, dizziness, sleepiness, and weakness as well as the usual effects of alcoholic intoxication manifested in speech, appearance and behavior. The duration of symptoms was from one to 12 days in those who recovered, one to three days in those who died. Residual blindness has persisted in one case now for over six months.

TREATMENT

Treatment recommended for methanol poisoning has included:

(1) Stopping further absorption of the methanol by removing the patient from access to it, and emetics or gastric lavage or giving charcoal by mouth.

(2) Increasing excretion by catharsis, especially with magnesium sulfate, diaphoresis by pushing fluids, hot drinks of all kinds, sodium bicarbonate, potassium acetate, sodium citrate, and other alkaline diuretics, hot packs and hot baths, enemas, etc., and stimulating pulmonary excretion by carbon dioxide inhalation.

(3) Lowering intracranial pressure by spinal puncture, fluid restriction and dehydration therapy, especially rectal or intravenous magnesium sulfate, intravenous hypertonic glucose or sucrose, etc.

(4) Alkalinization with sodium bicarbonate, sodium lactate, or other alkaline solutions both orally and intravenously, glucose and insulin, etc.

(5) Circulatory support by venesection, adrenalin, coramine, etc.

(6) Dietary replacement with vitamines, especially thiamine.

(7) Rest, general, and local rest to the eyes with eye shades or drawn window blinds, etc.

(8) Ethyl alcohol by mouth.

Scandinavian writers, impressed by the acidosis found in methanol poisoning cases, which they ascribed to the production of formic acid from the oxidation of the methanol, and by the possibility of "competition" for chemical combinations illustrated by the interference by para-amino-benzoic acid with the sulfonamides, suggested that the administration of ethyl alcohol might be of therapeutic value in retarding methanol oxidation. The fact that cases of methanol poisoning complicated by ethanol poisoning have shown a lower mortality rate than the uncomplicated methanol cases alone, was pointed out as supporting this belief. However, the combined cases usually represent the result of the use of methanol denatured ethyl alcohol, in which the methanol content is only about 4 or 5 per cent, so that the dosages consumed are much smaller. No evidence has yet been seen that there is any such "competition" for oxygen between ethyl and methyl alcohol. The data available indicates that the oxidation rates of the two alcohols are both limited and relatively constant. The data indicates also that they are not affected by each other (or by most other things, except serious liver damage) but that the oxidation rate of ethyl alcohol is more than five times that of methanol. Accordingly, since a normal man can oxidize only about 7 grams of ethanol per hour, the usual methanol oxidation must be only in the neighborhood of one ounce per day, and the formic acid production accordingly so small and slow as to be generally of little significance, except when it occurs in localities as in the eye where it is not readily removed.

EXPERIMENTAL DATA

Although the theoretical basis for the alcohol treatment of methanol poisoning thus appears dubious, the popular attractiveness of such a treatment made it desirable to check it further. Most workers have reported that ethyl alcohol is several times more toxic than methyl, despite the popular fear of the latter drug, but that the cumulative effect of methyl alcohol may make it more dangerous if repeatedly imbibed, and blindness from methanol poisoning undoubtedly occurs in a conspicuous fraction of those who consume methanol. Accordingly animal experiments were undertaken for this purpose. A total of 100 guinea pigs were used. Most of them had been infected previously with tubercle bacilli in connection with another experiment. Twenty-six were given ethanol, usually 30 grams, intraperitoneally, and 26 were given similar amounts of methanol, while 48 were given combinations of these two alcohols, in amounts totaling the same as that of the single doses in the previous sets. Altogether, 18 of the animals given ethyl alcohol alone died within six hours. Eighteen of those given the combined alcohols, and only eight of those given the methyl alcohol alone, died in this time. At autopsy there was still some unabsorbed alcohol present in the peritoneal cavity of most of the animals, and more would have died if the experiment had continued, but the greater toxicity of ethanol, and its futility in the treatment of methanol seemed evident.

SUMMARY

1. Methanol, or wood alcohol, poisoning may occur despite adequate labeling, warnings, educational campaigns, and measures to restrict the availability of the substance or to make it less attractive. All such preventive measures should be used, however, to lessen the frequency of these catastrophes.

2. Although less toxic than ethyl alcohol in acute animal experiments, its cumulative properties and

the amount and manner of its use results in a higher lethal rate among humans affected by it.

3. Symptoms of methanol poisoning generally resemble those of ordinary intoxication, but its more protracted course, greater frequency of eye symptoms, and especially the history of consumption of a suspicious liquor may lead to its recognition, which may be confirmed by laboratory tests. Many milder cases, however, go unrecognized. Treatments are directed especially at prevention of further absorption, increase in excretion and neutralization of the toxic effects of the methanol and its oxidative products, with especial attention to alkalinization, stimulation, lessening cerebral edema, and visual protection. The recommendation of ethyl alcohol in the treatment of methanol poisoning could not be supported by clinical or experimental observations.

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Comparative Roentgenographic and Microscopic Patterns in Bone Tumors*

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BONE tumors represent a group of neoplasms in which cooperative clinical and laboratory effort and acumen must attain their highest expression to achieve any satisfactory approach to accurate diagnosis and rational treatment. Pathologists, radiologists, and surgeons alike frequently regard the roentgenogram, the gross specimen and the tissue section as a fixed pattern, rather than a phase in neoplastic development modified by reactive changes in the tumor bed almost as variable as moving images on a screen. The kinetic concept of a developing pattern of morbid changes in tissue is, of course, fundamental in surgical pathology, and is of essential value in neoplasms of bone.

Some radiologists in recent years have suggested that diagnosis of bone tumors by radiographic methods is as accurate as by histological section. This untenable position has been fostered by diagnostic errors by microscopists, often due to the pathologist's failure to recognize that he should have complete historical, clinical and roentgenographic information on which to base his interpretation of cellular changes.

The radiographic changes and the gross appearance of bone tumors can be interpreted generally as a balance between the activity of the tumor, and the reactive stromal response evoked by the neoplasm. Specifically, the features of importance are osteolysis, its opposite phenomenon osteosclerosis, bone production either tumor or reactive bone, calcification, and vascular changes. The absence or degree of these features, their modification according to medullary, cortical or periosteal sites, the age of the individual, particularly in lesions involving epiphyseal areas, all contribute to the varying pattern which may be produced.

The classification presented here is an attempt to derive bone tumors according to their histogenesis. The relation between radiographic and histopathologic changes will be illustrated by cases from the connective tissue and giant cell groups.

Osteosarcoma is most commonly a sclerosing peripheral tumor. The striae which are frequently seen at right angles to the shaft represent new bone laid down in more or less parallel rows and are simply a phase in growth pattern which is by no means constant. Ordinarily, those osteosarcomas which form an osteoid matrix are exhibited roentgenographically as dense areas subperiosteal in location with elevation of the periosteum. The edge of the advancing periosteal elevation marks the advancing front of the tumor, and is known as Codman's reactive triangle. The aggressive, highly anaplastic and extremely vascular form of osteosarcoma is the aneurysmal form of osteolytic sarcoma.

But there are seldom pure examples of sclerosing or osteolytic forms, and some of these tumors exhibit equal tendencies toward both forms. Soft

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tissue extension may be attended by blotchy masses of radiopacity which are further new bone production.

Chondrosarcoma is also most often peripheral, and productive rather than sclerosing. The central lesions are usually destructive, but may be intensely sclerotic or eburnating. The outstanding histologic feature of chondrosarcoma is the calcification which takes place in the productive forms, which may produce blotchy masses, lobulated outlines, or may line up in parallel striae simulating osteosarcoma.

Fibrosarcoma is essentially an osteolytic process, seen in either early or advanced stages. In the latter, it frequently forms multiple pseudo-cystic areas, which belie their "cystic" nature because of the irregularity of the "cyst" wall as well as the adjacent reactive sclerosis. Still further advanced, this lesion exhibits a diffuse, linear sort of rarefaction, a ragged, moth-eaten appearance simulating advanced Ewing's sarcoma. Such tumors show a pure replacement of bone with fibrosarcoma. As in soft tissues, some fibrosarcomas differentiate toward osteoblastic structure and ossify, or develop areas of chondrosarcomatous material.

There is thus no pure pattern of bone neoplasms, nor can the radiologist distinguish with certainty between primary and metastatic lesions. A tumor of the distal end of the femur was so "characteristic" radiographically of osteosarcoma, that amputation was done without biopsy, but pathological examination showed it to be a metastatic adenocarcinoma, eventually proven to be primary in the prostate. Another bone lesion which by x-ray examination suggested either Ewing's sarcoma or a suppurative infection, proved on biopsy to be a metastatic carcinoma.

Giant cell tumors exhibit a multi-cystic structure, usually in epiphyseal areas, with distinct lines of demarcation from the unaffected bone. The periosteal contour is not destroyed or elevated, although it may be distorted by the expansile tumor. The histopathology is that of replacement of cancellous structure by tumor in a specific form, the epiphyseal chondromatous giant cell tumor of children, usually occurring in the upper end of the humerus, the microscopic picture may be alarming, but the radiographic appearance conforms to that of benign giant cell tumor elsewhere.

Thus the pathologist and radiologist are interdependent in the diagnosis of bone tumors. The final arbiter is the histopathologist, as he is in establishing any tissue change. He must, however, recognize that the intelligent diagnosis of bone lesions is inextricably associated with their radiographic appearance. The whole picture, with a clinical background, represents a pattern of neoplastic activity and response by the stroma of the host, which taken together are a summation of the neoplastic process which leads to accurate pathologic diagnosis.

MODERN TREATMENT REDUCES MENACE FROM TOXIC GOITER

"With judicious use of x-ray therapy in some instances, surgery in others, and a combination of iodine or thiouracil treatment with surgery in still others, the prospect for 100 per cent control of toxic goiter is indeed bright," writes W. W. Bolton, M.D., of the Bureau of Health Education, American Medical Association.

Dr. Bolton's article, appearing in the current issue of *Hygeia*, health magazine of the American Medical Association, states that "for many years, iodine was the only recognized specific treatment which was of any benefit in control of toxic goiter. But because it was not always effective, or perhaps kept thyroid activity reduced for a short time only, search for helpful measures continued. A genuine boom was introduced with development and refinement of surgical procedures. Techniques were devised for removal of enough of the thyroid gland so that what remained carried the body on a normal metabolic rate."

Another approach to the goiter problem is based on studies which have shown that the "secretion of the anterior portion of the pituitary gland, which is located deep within the skull, has a stimulating effect on thyroid function," the author says. "With this knowledge, in certain instances when signs of thyroid hyperactivity appear, it is possible to reduce output of pituitary secretion and remove its whipping effect on the thyroid by x-ray treatment of that gland."

The author points to thiouracil as another late development in the control of excessive thyroid activity. "This chemical, first investigated in 1943, has the power to bring about, often in an amazingly short time, prompt subsidence of thyroid activity to normal. Best of all, once the hyperactivity has been checked, the gland shows no tendency to 'run wild' again, even though use of thiouracil may be discontinued. Final evidence regarding thiouracil has not yet been obtained. It is a potent drug, and indications are that it must be used cautiously and under constant medical supervision.

"Even more recent is the use of radioactive iodine produced by the use of cyclotron," he says.

MEDICAL PROGRESS:

Recent Progress In The Treatment Of Thrombo-Embolic Disease

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INTEREST in the problems of venous thrombosis and pulmonary embolism has increased rapidly during the past decade. This interest has been stimulated to a great extent by the controversy which has arisen as to the best method of prevention and treatment. The heat of controversy has fortunately been accompanied by considerable light shed upon the fundamental problems involved. Equally fortunate for patients suffering from these conditions is the fact that these new therapeutic measures have all brought great reductions in morbidity and mortality in comparison with the results obtained by the time-honored expectant treatment of rest, elevation and the application of heat.

Primary consideration in the treatment of thrombo-embolic disease should necessarily be given to reducing the mortality from pulmonary embolism. Of importance also are efforts to decrease the morbidity from thrombosis and the disabilities arising from thrombophlebitis.

INCIDENCE

Consideration of the incidence of thrombosis and pulmonary embolism serves to call attention to the conditions under which these complications are likely to arise. The percentage of cases of thrombo-embolism encountered in the course of routine hospitalization is small. In 172.888 records of surgical patients at the Mayo Clinic[6] only 0.96 per cent suffered this complication. The incidence in 125.524 postoperative cases reported by Zilliacus[50] was 0.51 per cent. In selected groups of patients, however, such as those subjected to extensive abdominal operations for cancer, abdominal hysterectomies, prostatectomies and operations on the biliary tract the number of cases increases considerably. Crafoord and Jorpes[16] report a 9 per cent incidence of thrombo-embolism in 1,111 cases of this nature. Murray and Best[36] have shown a similar high incidence in patients operated on at the Toronto General Hospital. Pulmonary embolism has been found to be the most common cause of death after fractures of the hip by Golodner, Morse and Angrist.[24] The increased incidence of pulmonary embolism in obese patients first pointed out by Snell[45] has been emphasized by Ochsner.[38]

When careful search for antemortem thrombosis has been made in the course of postmortem examinations in an unselected group of cases, an astonishingly high incidence of intravascular thrombosis has been found. Rössle[42] found that the veins of the calf harbored thrombi in 27.1 per cent of 324 patients over 20 years of age. In their first report, Hunter[30] and his colleagues found thrombosis of the deep veins of the leg in 52.7 per cent among 351 middle-aged and older persons forced to bed for varying periods of time. Pulmonary embolism, however, was the cause of death in only 3.13 per cent of the deaths. It is highly probable that intravascular thrombosis occurs far more frequently than it is recognized and that many cases subside spontaneously without complications.

Analysis of the cases of fatal pulmonary embolism with respect to the clinical condition from which the patient was originally suffering calls attention to the wide field in which the problem of thrombo-embolism is present. Only 40 per cent of the 370 cases studied by Hampton and Castleman[25] followed operation. Cardiac disease was a predisposing factor in 30 per cent and patients suffering from general medical conditions accounted for the remaining 30 per cent. As Hunter[31] has remarked, "The greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person."

Whereas the incidence of thrombo-embolism is relatively low in the general run of clinical conditions, once intravascular thrombosis has occurred, as manifested by thrombophlebitis, phlebothrombosis or pulmonary infarction, the frequency of subsequent pulmonary embolism is alarmingly high. In 897 cases of thrombophlebitis reported from the Mayo Clinic by Allen, Barker and Hines,[4] subsequent pulmonary embolism occurred in 15.6 per cent and the embolus was fatal in 5.7 per cent. In 678 patients who survived an initial pulmonary embolus, subsequent embolism took place in 30.5 per cent and in 18.3 per cent fatal pulmonary embolism occurred. Bauer[9] over a ten-year period observed a mortality from pulmonary embolism of 18 per cent in 264 cases of thrombosis. The significance of these findings was emphasized by Barker[6] and his co-workers: "If all fatal embolisms which were preceded by a clinically diagnosed nonfatal embolism could be prevented, the total number of fatal embolisms would be reduced by more than a third." If, in addition, all the clinically recognizable cases of thrombosis could be satisfactorily treated, the incidence of fatal pulmonary

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embolism might be reduced to a considerable degree.

Two problems in diagnosis arise in thrombo-embolism, that of intravascular thrombosis and that of pulmonary embolism.

Thrombosis. The location of the intravascular thrombosis in the great majority of cases has been in the lower extremities. From combined clinical diagnosis and incidental necropsy findings 96.8 per cent of the cases were found by Allen, Barker and Hines[4] to involve the veins of the lower extremities. Bauer[9] believes that the origin of the thrombosis in thrombo-embolic disease is in the lower extremities in 98 per cent of the cases. Early diagnosis of thrombosis in the veins of the leg is therefore to be sought. It is important at this time to emphasize the difference in the clinical picture presented by thrombosis occluding the femoral and iliac veins, the so-called phlegmasia alba dolens, with its readily recognizable swelling, pain and fever, and the more insidious thrombosis originating in the veins of the foot or calf. This latter condition Homans[27] has termed "deep quiet venous thrombosis" while Ochsner and DeBakey[39] have identified it as "phlebothrombosis." Bauer[9] prefers the designation "acute thrombosis of the deep veins." Distinction between the two conditions is important since the bland thrombosis starting in the leg frequently gives no signs or symptoms of its presence until pulmonary embolism occurs. The first indication of venous thrombosis in 41 per cent of the 202 cases reviewed by Allen, Linton and Donaldson[1] was pain in the chest. Of greater significance in the early diagnosis of thrombo-embolic disease in their patients was an unexplained simultaneous elevation of the temperature, pulse and respiration on the clinical chart. This sign was the first one noted in 81 per cent of their series. Careful examination of the legs in all patients in the older age group who are confined to bed should be a routine daily practice. Tenderness over the calf, increased warmth of the skin over the calf or foot and pain or restriction of motion on dorsiflexion of the foot, which Homans[28] calls the "dorsiflexion sign," may indicate early thrombosis in the deep veins of the leg. Observation of the difference in the rate of drainage of blood from the soles of the feet upon moderate elevation has, in my experience, been useful in detecting early changes in the efficacy of venous outflow. A method of differentiating the tenderness due to thrombosis of the veins of the calf from tenderness of the muscles due to other causes was suggested by Moses.[34] He first examines the deep structures of the calf by pressure with the tips of the fingers. Tenderness elicited by this procedure is then compared with that produced by lateral pressure on the calf muscles. Phlebography, once advocated for the early diagnosis of deep thrombosis of the leg, has not been found a reliable means for establishing the diagnosis in the hands of most observers. Phlebograms are difficult to interpret and spasm of the larger veins, which has clearly been demonstrated by Papper and Imber,[41] may be misleading. Bauer,[10] on the other hand, has developed a standard technique whereby the deep veins of the leg, particularly the peroneal veins, are filled by a slow injection of contrast medium into the short saphenous system. The vein is exposed by a small incision behind the lateral maleolus and the needle temporarily tied in place. Films are taken in two planes at 50 and 60 seconds during the injections. His studies on the pathogenesis of thrombosis of the deep veins of the leg have been an outstanding recent contribution.

Pulmonary Embolus. Since pulmonary embolism is frequently the first clinical evidence of intravascular thrombosis, early diagnosis of this condition is urgent in order to prevent recurrence. The classical picture of sudden pain in the chest, dyspnea and hemoptysis is by no means universal. Nor is it necessary for the patient to have been confined to bed. Homans[28] was the first to call attention to the development of pulmonary infarction in apparently healthy adults. Careful examination was necessary in order to disclose the site in the legs from which the emboli arose. Hampton, Prandoni and King[26] have reported ten cases of pulmonary embolism from obscure sources. The patients were all healthy adults who were admitted to the hospital for acute pulmonary conditions. The diagnosis of pulmonary infarction was made on the basis of x-ray examination of the chest, electrocardiogram and phlebography. Except in one of the cases, there was no obvious sign of venous thrombosis. Recovery took place in all patients following treatment with anticoagulants. The x-ray diagnosis of pulmonary infarction has been carefully investigated by Hampton and Castleman,[25] both in the living patient and at autopsy. The site of lodgement of the embolus was in the lower lobes in 74 per cent of their cases with slight preferment for the lower lobe on the right side. They have stressed the fact that the area of infarct is always in contact with one of the pleural surfaces and that the border towards the heart when viewed from the correct angle always presents a peculiar "hump." Embolism need not produce infarction. In a number of their cases spontaneous resolution occurred. To this process they have given the term "incomplete infarction." Because of the changing appearance over a short space of time they advocate repeated examinations in cases who are suspected of having suffered a pulmonary embolus. Repeated electrocardiographic examinations are indicated in the doubtful cases for the same reason.

ETIOLOGY AND PREVENTION

Three etiological factors responsible for thrombosis have been emphasized by deTakats and Fowler,[18] slowing of the circulation, changes in the vessel wall and increased coagulability of the blood. Methods of prevention will be considered in the light of these etiological factors.

Slowing of the circulation. Since it is recognized that confinement to bed of a previously ambulatory older person is the most important

predisposing factor in thrombosis, active exercise, especially of the legs, is strongly advocated. Hunter[31] and his associates found that the incidence of thrombosis noted at postmortem examination was reduced to one-third by the institution in the medical department of exercises for the patients. Shaw and Richards[44] found that post-operative embolism was reduced to one-fifth by the institution of regular exercise periods. The importance of supervised exercise in the postoperative period was stressed by Ochsner.[38] At the times that the patient is having his pulse and temperature taken by the nurse he should routinely raise and extend his feet at the ankle. The tight sheets of the neat hospital bed, though esthetically satisfying, facilitate the development of thrombosis by extending the feet and thus producing maximal relaxation of the flexor muscles of the calf. With the patient on his side, however, active movements of the lower extremities can be readily carried out without the production of pain. Even in case that the patient's leg is enclosed in a plaster cast, he can still obtain the advantage of muscular activity by alternately contracting and relaxing his muscles. Bauer[11] has urged this form of exercise, which is particularly important after injuries of the lower extremities, since he has shown that the incidence of thrombosis is in these cases as high as 12 per cent.

It was hoped that "early ambulation" in the postoperative period would bring about a decrease in the incidence of thrombo-embolism. As this procedure is not frequently being carried out, these hopes have not been realized. In fact Blodgett and Beatty[12] have shown that the incidence of thrombo-embolism may actually be increased. Since it is the actual movement which appears to have a beneficial effect and since simply sitting in a chair by the bedside promotes stasis in the veins of the leg it would appear to be a better policy to have the patient get out of bed, walk about a short time and get in again. Once the patient is fully ambulatory and can walk to and fro, the need for supervised exercise is past.

Other measures designed to improve the circulation have been advocated by numerous observers. The importance of elevating the foot of the bed to prevent venous stasis has been repeatedly stressed. Application of pressure to the legs by means of compression bandages in all patients over the age of 45 who undergo an extensive operative procedure has been advocated by Ochsner.[38] It is a logical form of prevention since compression will empty the veins in which blood is not flowing and will speed-up the flow of blood in veins which are carrying the blood to the heart. This compression treatment, which was first advocated by Fischer[23] is especially useful for acute thrombophlebitis. Rapid subsidence of the inflammatory process is facilitated. The exact means by which compression favors resolution is obscure but it may depend upon improving the distribution of blood flow to the peripheral tissues. Chapman and Linton[15] have suggested an explanation of the mechanism by which emboli are broken off to be carried to the lungs during activities associated with straining movements on the part of the patient with the glottis closed. They believe that forceful expiration under these conditions, the so-called Valsalva experiment, causes a sudden backing up of the venus stream with ballooning out of the great veins of the lower half of the body. With the subsequent sudden release of pressure associated with inspiration, the venous pressure falls sharply and if there is a poorly organized thrombus floating in one of the larger veins it may become detached or a part may be broken off during these abrupt changes in venous pressure.

Another factor which is probably of significance in the retardation of the circulation is reflex vasoconstriction due either to temperature changes or to the traumatic stimuli associated with the illness or operative procedure. The increased incidence of thrombo-embolism during the winter months has been noted by Allen, Linton and Donaldson.[2] Naide and Säyen[37] have found that the proportion of patients who had previously developed thrombophlebitis who exhibited an abnormally high vascular tone was greatly in excess of normal. It is likely that vasoconstriction which affects the veins as well as the arteries may be of real signifiance in promoting vascular stagnation.

Endothelial damage. Thrombosis is naturally favored by damage to the intima of vessels though efforts to relate this fact to clinical conditions have been disappointing. Jensen[32] has demonstrated pathological changes in the walls of veins at a level considerably above the region where thrombosis has occurred. Attempts by Tannenberg[46] to produce thrombosis from allergic reactions in the walls of veins by the administration of bacterial toxins in sensitized animals were unsuccessful. Gross trauma to veins will produce thrombosis and this thrombosis can be prevented by regional or general heparinization as shown by Murray and Best,[36] but the importance of this factor in initiating clinical thrombosis is not yet clear. It seems likely that the high incidence of thrombosis in the leg after trauma noted by Bauer[11] is dependent upon direct injury to the vessels.

Increased coagulability of the blood. Increased coagulability of the blood following trauma and operations has long been recognized. Wright[49] has recently demonstrated not only an increase in the number of platelets in the circulating blood after operations or child-birth but also an increase in the adhesive quality of the platelets. Anticoagulants reduce the adhesiveness of the platelets. An increase in the concentration or activity of prothrombin has been demonstrated by Brambel and Loker.[13] They found that by using plasma diluted to 12.5 per cent they were able to demonstrate finer variations in the prothrombin time in the blood. Significant increases were observed after operations and after delivery. Of particular significance were their findings of increased prothrombin activity in cases of phlebitis and after stopping the administration of dicou-

marol. Shapiro[43] suggested the use of this test in differentiating pulmonary embolism from other conditions. He advocated its use in the selection of cases in whom thrombo-embolism was likely to occur. Increased tolerance to heparin following operations was first noticed by Crafoord and Jorpes[16] when they began to use this substance prophylactically in surgical patients. The heparin tolerance test to select patients who might be subject to thrombo-embolism was suggested by deTakats.[19] According to this test the clotting time is measured with a capillary tube 10, 20 and 30 minutes after the intravenous injection of 10 mgm. of heparin. The heparin tolerance was found to increase for the first 3 to 4 days after operation.

Comment. Although recent reports on altered coagulability of the blood as a predisposing factor in the origin of thrombo-embolism are highly suggestive, they do not yet offer much help from the standpoint of prevention. The laboratory determinations are difficult and require highly trained technical assistance. Although the observations are extremely interesting and important for an understanding of the pathogenesis of thrombo-embolism no laboratory test has yet been devised by means of which the individual who will develop intravascular thrombosis can surely be identified.

PROPHYLACTIC TREATMENT

Over the question of the best method of prophylactic treatment of thrombo-embolism the controversy has been the most active. Since both vein ligation and the use of anticoagulants have yielded excellent results in reducing the mortality from pulmonary embolism the advocates of each method have vigorously insisted upon the advantage of their method. Enough time and a sufficient number of cases have now accumulated so that an appraisal can be made.

Vein ligation. All who have had the unhappy experience of watching a thrombosis of the calf ascend and even terminate with a fatal pulmonary embolus cannot help but be impressed with the dramatic results which follow ligation of the vein ahead of the propagating thrombus. Similarly, in the patient who is desperately ill after repeated sub-lethal pulmonary infarcts, the rapid improvement when the vein through which these emboli pass is safely tied off, marks this procedure as a life-saving measure. Allen[3] has recently summarized the results of interruption of the femoral veins in 816 patients at the Massachusetts General Hospital. There was but one death from massive pulmonary embolus following this procedure. Because of the high incidence of involvement of the veins of both legs, bilateral ligation was practiced with rare exceptions. In the last year for which statistics were available 98.2 per cent of the ligations were bilateral. This procedure was used for prophylactic purposes in an increasing number of cases, so that in 1945 over one-third of the ligations were performed for this reason. The indications for ligation in the remaining cases were approximately equally divided between pulmonary embolism and venous thrombosis in the legs. Numerous reports have come out on ligations of the veins at higher levels, common femoral (Fine and Starr[22]), iliac (Bancroft,[5] and Homans[27]) and vena cava (Veal and Hussey,[47] O'Neil[40] and Moses[35]). Although there may be occasional instances in which ligations at these higher levels are indicated, the very fact that anticoagulants have had to be used[5,20] after these high ligations in order to prevent further thrombosis and embolism casts doubt on the necessity and the advisability of such radical procedures. Although ligation of the superficial femoral vein distal to the profunda is seldom followed by signs of venous impairment, ligation of the common femoral vein may have disastrous results. Dennis[17] has reported such a case and Homans[29] states that he has encountered two similar ones. deTakats and Fowler[18] find that ligation of the femoral vein above the profunda invariably results in considerable edema. Although ligation of the common iliac vein and even of the vena cava may allow for a better development of collateral circulation, and Veal and Hussey[47] have commented on the remarkable restoration of function which occurs after ligation of the vena cava, yet accurate studies show the degree of venous insufficiency which follows interruption of the veins at such high levels. Burch and Winsor[14] studied the venous pressure in the feet of five patients in whom the inferior vena cava was ligated for septic phlebitis. All but one of the patients showed edema up to ten months after operation and the venous pressure in all cases was considerably increased with diminution in the digital oscillations. They found, however, that there had been remarkable compensation. Allen[3] in summarizing the experience with vein ligation at the Massachusetts General Hospital, has concluded that "common femoral vein interruption is not recommended in spite of one fatal embolus from the profunda femoris vein after superficial femoral interruption. Serious sequelae can occur under certain circumstances from common femoral vein occlusion. The technical difficulties far outweigh any added protection to the patient."

Comment. Vein ligation has a very significant place in the treatment of thrombo-embolism. It is especially called for in patients who have had a warning emoblus and in whom careful examination reveals signs of thrombosis in the leg. Under such circumstances both superficial femoral veins should be ligated. Again, evidence of thrombosis in the leg in a patient who for some reason cannot be mobilized calls for bilateral superficial femoral vein ligation. Finally, in cases that the use of anticoagulants is contraindicated, vein ligation may be a life-saving measure. Because of the high incidence of embolism after vein ligation in case that the thrombosis has extended above the superficial femoral vein, there appear to be few indications for ligation above this level.

ANTICOAGULANTS

Heparin. Many favorable reports on the use of anticoagulants for the prophylaxis and treatment of thrombo-embolism have been published. With the use of heparin by continuous intravenous drip, Murray and Best[30] in 1938 reported the successful prophylactic treatment of 315 surgical cases without a single case of thrombo-embolism. Furthermore, in seven cases of pulmonary embolism and 28 cases of thrombophlebitis there was no recurrence. Crafoord and Jorpes[16] in 1941 presented the results they had obtained by the use of heparin given in repeated intravenous injections four times daily. The incidence of thrombo-embolism in over 1,000 cases in the control series was 9 per cent. With the use of heparin in 325 cases there was not a single instance. Bauer[9] has recently summarized his experiences with the administration of heparin in the treatment of thrombosis and embolism over a five-year period. Before the use of heparin, in 264 cases in which the diagnosis of thrombosis had been made, there were 47 deaths, a mortality of 18 per cent. During the five years, with the use of heparin, the diagnosis of venous thrombosis was made and generally confirmed by phlebography in 209 cases. There were but three deaths, a mortality of 1.4 per cent. Only one of these patients was under the influence of heparin at the time of the fatal embolism. Bauer[9] has outlined a plan for the treatment of thrombo-embolism which is commendable for its efficacy and simplicity. The general principles of this plan are essentially (1) early diagnosis, (2) immediate heparinization, (3) active exercises of the legs from the beginning, and (4) early mobilization during the period of heparinization, with a tapering off of the administration of the drug. An initial dose of 150 mgm. of heparin is injected intravenously as soon as the diagnosis is made, followed by one or two more similar doses the first day, depending upon the time of day in which the treatment is started, but never at closer intervals than four hours. On subsequent days the patient is generally given 150 mgm. at night and in the morning, with 100 mgm. at midday. In the mild case this active heparinization is continued for but three to five days and the dosage is then tapered off by omitting one or more doses each day. In the presence of massive pulmonary embolism or extensive thrombophlebitis larger doses of heparin are required. If the patient is not ambulatory the treatment is carried on for a longer period of time. Bauer[9] has emphasized the fact that recurrence of the thrombosis and embolism is apt to occur if the drug is withdrawn too suddenly, and he has strongly advocated the early mobilization of the patient while under the influence of the anticoagulant. Not only was the incidence of pulmonary emoblism reduced to low levels by this form of therapy but the process of thrombosis was definitely arrested. In case that the venous system of the lower leg alone was involved at the time treatment was started and the process arrested at this point, the development of collateral venous circulation was most satisfactory and the resultant post-phlebitic difficulties minimal. In case that the femoral vein was already involved at the time the anticoagulant was started, some disability generally resulted. Early treatment with heparin not only lowered the mortality to one-tenth but the period of hospitalization was greatly reduced. Complications from bleeding were rare with this form of treatment, there being three cases of hematuria and two patients who developed hemarthrosis. It is interesting to note that Bauer does not mention the necessity of controlling the dosage of heparin by determinations of the clotting time. It is well known that the depression of the clotting time following intravenous administration of heparin is not evenly sustained (Walker[48]) and so with this intermittent type of administration there must be periods during the 24 hours when the patient is not protected against intravenous thrombosis. On the other hand, the clinical results reported with the intermittent heparinization are so uniformly favorable that the need for continuous administration may be questioned, especially since the complicating factor of hemorrhage may be avoided by the less intensive form of treatment. Administration of heparin in Pitkin Menstruum, a form which allows it to be slowly released over a two-day period, has been developed by Loewe[33] and his associates. Favorable results with this form of treatment were reported in 125 cases, although there were four cases of fatal embolism. They advocated prolonged treatment, 10 to 14 days for uncomplicated thrombophlebitis and three to four weeks after pulmonary embolism. The need for such prolonged therapy may be questioned, especially in case that active mobilization is feasible after a short period of heparinization. The use of heparin/Pitkin in combination with dicoumarol has been advocated by Evans and Boller.[21] The two drugs are given simultaneously and the heparin effect on the clotting time wears off at just about the time that the depressant effect of the dicoumarol on the prothrombin level becomes effective.

Comment. Heparin, according to all reports, is effective in the prevention of thrombo-embolism. Its action in arresting the process of intravascular thrombosis is especially desirable. It is, however, expensive and its administration cumbersome. Control of the dosage by determinations of the clotting time is not difficult and the occurrence of complicating hemorrhage has been reported only rarely.

Dicoumarol. Dicoumarol, the hemorrhagic agent from spoiled sweet clover first isolated and synthesized by Link, prevents the formation of prothrombin in the liver. It has been extensively used in the prevention and treatment of thrombo-embolism. In 1,000 cases reported by Barker, Cromer, Hurn and Waugh[7] from the Mayo Clinic, there was but one death from pulmonary embolism and this embolism occurred after the prothrombin had returned to normal because the

Dicoumarol had been given for insufficient time. This record is the more impressive since Dicoumarol was used in 379 cases of thrombosis or embolism in which the incidence of subsequent thrombo-embolism is so high. This drug is given by mouth, 200 mgm. to patients under 150 lb. in weight and 300 mgm. in those who weigh over 150 lb. The prothrombin time must be accurately checked before the administration of any more Dicoumarol since 27 per cent of 340 consecutive patients studied by Barker and his associates were hypersensitive to the drug. In cases of hypersensitivity the prothrombin may fall to less than 10 per cent of normal after the first one or two doses or after subsequent doses. Serious bleeding may take place under these circumstances. The full effect of the administration of Dicoumarol does not occur for 24 to 48 hours and sometimes even longer. Again, the prothrombin deficiency may continue for from two to ten days after the last dose of Dicoumarol has been given. Barker and his associates recommended that the prothrombin level be kept between 10 and 30 per cent of normal by the administration of 200 mgm. of Dicoumarol on each day that the prothrombin was greater than 20 per cent of normal. In the first 497 cases in whom Dicoumarol was used postoperatively to prevent thrombo-embolism Barker, Allen and Waugh[8] reported bleeding of some degree in 47, an incidence of almost 10 per cent. In 4 per cent the bleeding was more than slight and there was one fatality. In this case the prothrombin time was only 28 seconds, so that the part played by Dicoumarol in the production of this fatal hemorrhage may be questioned. In all the remaining cases of moderately severe or severe bleeding the prothrombin time was in excess of 60 seconds. Evans,[20] in reporting on the use of Dicoumarol in 55 cases encountered hemorrhages in eight patients with two fatalities. In a recent report[21] he has reduced the dosage of Dicoumarol to 100 mgm. and this dose is given only after the prothrombin time has been found to be above 65 per cent. deTakats[18] attempts to maintain the prothrombin level between 60 and 30 per cent. Prothrombin deficiency due to the action of Dicoumarol can be effectively counteracted both by transfusions of fresh whole blood and by the intravenous administration of synthetic vitamin K in the form of Menadione bisulfite. According to Barker,[7] a single dose of 64 mgm. was sufficient in 35 of the 37 patients who were treated for this complication, to bring the prothrombin time down to a safe level. The possibility of precipitating a recurrence of thrombosis with such large doses should be kept in mind. deTakats[18] has reported two cases in whom fresh vascular accidents appeared to coincide with the administration of the vitamin.

Of great interest is the recent report by Allen[3] on the use of Dicoumarol in small dosage for the prevention of thrombo-embolism at the Massachusetts General Hospital. In a well-controlled series of 101 cases, 200 mgm. of Dicoumarol was administered to patients between the ages of 40 and 65 on the second or third day after operation. In ten patients in this series a second dose of Dicoumarol was given. There were but three instances of thrombo-embolic complications and in two of these the dosage of Dicoumarol had no appreciable effect on the prothrombin time. In the control group who "were comparable in every respect to those in the same age group receiving Dicoumarol" there were 14 instances of thrombosis requiring vein interruption. In those receiving Dicoumarol there were no undesirable sequelae which could be definitely attributed to the use of the anticoagulant. Although this series is too small for the results to be statistically significant, the observations are extremely interesting in that they suggest the possibility of administering Dicoumarol in dosage small enough not to produce the complication of hemorrhage but yet sufficient to reduce very substantially the complication of thrombo-embolism. In addition, the small dosage given may permit the routine administration of Dicoumarol without the necessity of the highly specialized determination of the prothrombin time.

Comment. There are numerous contraindications to the use of Dicoumarol: (1) hepatic or renal disease, (2) blood dyscrasias, (3) recent operations upon the brain, spinal cord and thorax in which postoperative hemorrhage may be hazardous, and (4) granulating wounds or conditions requiring drainage from the gastrointestinal tract. Again, prophylactic use of Dicoumarol is hardly feasible in patients confined to bed for prolonged periods of time because of cardiac, pulmonary or other serious medical conditions. In addition, because the individual reaction to Dicoumarol is unpredictable, this anticoagulant should not be given in large doses unless facilities are available for accurate determinations of the prothrombin level. Dicoumarol is easier to give than heparin; it is less expensive and the effect lasts longer. Complications from hemorrhage are more frequent than with the use of heparin, according to reports from the literature. Just as with heparin, thrombo-embolism may recur after discontinuation of the drug. All those who have used Dicoumarol have for it a healthy respect. Under strict control it has been a great boon, but without constant vigilance it can be a serious threat to the life of the patient.

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EDITORIALS

The Clinical Significance of Protein

The important role of protein nutrition in medicine has been stressed in abundant clinical and experimental reports. Although they are related to protein intake, we will not consider here the roles of fluid and electrolyte balance and vitamin intake, but rather of protein per se.

Proteins, whether derived from animal or vegetable sources, are designated as "complete" if they contain those amino acids which the body is unable to synthesize. Optimal nutrition, as far as protein intake is concerned, is usually considered to be one gram per kilogram of body weight per day for adults, and three to four times that amount for infants and children. All ingested protein is split by the pancreatic enzymes into polypeptides and ultimately into amino acids—in which form they enter the portal blood. The amino acids may be converted to carbohydrates, or may be used as building blocks for the formation of body or plasma proteins. The liver plays a dominant role in these processes. All nitrogen excreted by the kidneys is from either this ingested (or exogenous) protein, or the breakdown of body (or endogenous) protein. Nitrogen loss in the stools is highly constant in health. In disease protein may be lost in the urine, from the surface of burns, or areas of suppuration. An individual is in nitrogen balance only if his nitrogen (i.e., protein) intake is equal to the total nitrogen loss from all routes. If nitrogen loss exceeds the intake, the inference is inescapable that tissue proteins are being destroyed to meet the demands and the person is in "negative" nitrogen balance.

A clinical suspicion of protein deficiency may be obtained by scrutiny of the patient's dietary history, both as to protein and caloric content, for if the latter is inadequate body proteins are burned to furnish energy and loss of weight will result. If a decrease in plasma proteins is detected gross protein deficiency is present. In this connection we should recall that Elman[7] has calculated that in an adult of 70 kilograms for each gram per cent that plasma proteins decrease, a total body loss of fully one thousand grams has occurred.

Protein deficiency may result from inadequate intake (as in famine); inadequate absorption (as in chronic diarrhea or absence of pancreatic ferments); or inadequate utilization (as in cirrhosis of the liver). The heightened metabolism of fever or hyperthyroidism increases the need for protein as does the developing fetus in pregnant women. Excessive loss may be occasioned by the exudate of severe burns or infected wounds, or the albuminurea of nephrosis.

A few specific illustrations may make these generalities more vivid. Excessive urinary nitrogen loss representing a negative balance of 50-150 gm. of body protein per day may follow with fractures,[5] burns,[8] or relatively simple surgical procedures. Gastrointestinal surgery results in an added strain on protein stores because of the patient's inability to assimilate food. Wounds heal less rapidly when hypoproteinemia is thus allowed to develop[9] and this lack of satisfactory repair likewise involves, of course, internal suture lines such as at the site of gastrointestinal anastomoses.

In non-surgical realms, the anemia of pregnancy is frequently accentuated by protein lack,[2] hypoproteinemia is present in a major portion of patients with severe thyrotoxicosis[1] and in patients with cirrhosis of the liver. Peptic ulcers are reported to be more readily healed by feedings of a protein digest, rather than the traditional Sippy regime.[4] Here, however, we should recall that many other factors are present in the complicated ulcer problem. In stenosing duodenal ulcer, with associated anorexia or frank vomiting, plasma proteins are soon distinctly lowered. The prompt utilization of small frequent feed-

ings of a protein digest, may correct the hypoproteinemia and hence tend to relieve the element of edema which is present at the scarred pylorus.

Whether an oral or parenteral protein is given will obviously depend on the nature of the disease, the magnitude of the deficiency, and the urgency of promptly meeting the protein deficit. The amino acids now available for protein therapy are derived from either the enzymatic or acid hydrolysis of casein, lactalbumins, or pancreas. Tryptophane is added to the products obtained by acid hydrolysis to render them complete. The oral preparations are palatable and the parenteral solutions so purified that reactions from their intravenous use is infrequent. The more concentrated oral products range in protein content from 70 per cent to 90 per cent. In general, when a case demands sustained parenteral glucose for nutrition it will prove desirable to give 5 per cent hydrolysates intravenously as well. In patients with vomiting, pronounced diarrhea, or enteric fistulae, parenteral amino acid therapy will be necessary. However, unless pain, toxemia or anorexia prevent an adequate intake, oral therapy will suffice in most all other instances. As much as 300 gm. of protein may be taken by mouth and assimilated readily. These oral preparations are fully acceptable to the patient in milk, fruit juices, or soup and serve as ideal supplements to the usual "high protein" hospital diet.

Plasma may be administered in protein deficiency, but its major use in connection with shock is not pertinent to this discussion. However, it should be re-emphasized that mere protein therapy must be complemented by full attention to other nutritional needs.

The integrity of the liver is paramount in the ultimate utilization of proteins no matter by what route they are administered. Thus in severe hepatic cirrhosis high protein diets usually fail to significantly elevate the plasma level. Conversely, the liver is more prone to be damaged by poisons, as chloroform,[6] when deficient in protein.

Many further points of clinical interest will surely be forthcoming in this field. One deserving mention is the work of Cannon[3] which indicates that antibody formation is less active in persistent protein deficiency. The demonstration of the inter-relationship of these many facets of protein nutrition will continue to be an exciting and important sphere of clinical and experimental investigation.

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Penicillin Treatment of Resistant Subacute Bacterial Endocarditis

Subacute bacterial endocarditis caused by nonhemolytic streptococci of various types has been a uniformly fatal disease. Recent investigation has demonstrated that the infectious process can be eradicated in nearly all cases of this disease if penicillin is administered in sufficient amounts and for an adequate length of time.[1,2,7]

It is now generally agreed that uninterrupted treatment for not less than four and preferably for six to eight weeks is necessary if optimum results are to be obtained.[1,6] Penicillin may be administered in such cases continuously by the intravenous or intramuscular route.[5] Equally and, perhaps, more satisfactory clinical results are obtained if the drug is injected intramuscularly at three-hour intervals.[4] This technique is much more simple and usually preferred by the patient.

The amount of penicillin which must be given during each 24-hour period is less clearly defined. In general, there is a rough correlation between the concentration of penicillin necessary for the complete inhibition of the infectious agent *in vitro* and the required daily dose. The streptococci isolated from the majority of cases of subacute bacterial endocarditis are inhibited by 0.1 unit of penicillin per ml.[3] Under these circumstances the daily administration of 300,000 units of penicillin will usually be adequate for the elimination of the infection.[1]

If the infecting streptococcus is more resistant larger amounts of penicillin must be used. No definite recommendations may be made at this time as to the minimum dosage which will be effective with organisms of increasing degrees of penicillin resistance. Each case must be managed individually. The initial daily dose should be 500,-

000 to 1,000,000 units. The dosage should be increased progressively in increments of approximately 1,000,000 units per day until the blood cultures are persistently sterile and all clinical signs of activity have disappeared. Such a regime will be followed by bacteriological cures in nearly all patients, but enormous quantities of penicillin may be required. Thus 5,000,000 to 20,000,000 units of penicillin per day have been administered[6] and even larger dosage will certainly be necessary in certain cases.

The fact that a number of patients suffering from subacute bacterial endocarditis caused by moderately penicillin resistant nonhemolytic streptococci have recovered following the utilization of massive doses of penicillin when previous regimes employing smaller amounts had failed demonstrates that no person suffering from this disease may be regarded, on *a priori* grounds, as unsuitable for antibacterial therapy. On the contrary, the evidence suggests that adequate treatment will be followed by eradication of the infection in nearly every case.

A special and nearly unique problem has been presented to the medical profession since one to five thousand dollars or more may be required to purchase penicillin at wholesale prices for the cure of subacute bacterial endocarditis caused by resistant organisms. These costs are frequently too great to be borne by the individual patient or by the funds at present available for the purpose in clinic and free hospitals. A purely economic barrier may, therefore, stand between the sick individual and the utilization of adequate therapy which may be expected to lead to recovery.

Suitable action on the part of the medical profession is imperatively required in order that funds may be made available for the treatment of these difficult cases of subacute bacterial endocarditis.

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New Industrial Accident Fee Schedule

Through the prolonged and painstaking efforts of a special committee of the California Medical Association, the Industrial Accident Commission has recently adopted a new and complete fee schedule. It became effective November 1, and copies have been sent to all members of C.M.A. The schedule provides an increase of approximately 25 per cent over the old schedule (or of approximately 9 per cent over the existing temporary one which consists of the old schedule plus a 15 per cent surcharge.)

It is anticipated that some insurance companies may attempt to circumvent the new schedule by making private contracts with individual physicians. Your Association believes that the new schedule, especially in view of current inflation, is reasonable, and will permit all properly conducted insurance companies to continue to make a fair profit on their projects. Therefore, your Association urges each member to "stand by his guns" and adhere to the schedule as printed. In this manner, fair medical fees will be obtainable for competent work, and the tendency to maintain a high quality of work will be encouraged.

Some county societies may well decide to request members who arrange private contracts for industrial work to submit copies of those contracts to their Committees on Professional Conduct for review. This is a matter for decision by each individual county unit.

The new schedule, like all fee schedules, is not believed to be a perfect document; it is and should be subject to periodic review and constructive readjustment. Your suggestions to the Fee Schedule Committee of your county or state association will be respectfully received in this connection.

Clinical-Pathological Conference*

This 37-year-old white, American housewife entered Lane Hospital 11/10/42 with complaint of swollen ankles.

Present Illness: At about age 21, patient had a "cold" followed by pain in the flanks. Similar episodes recurred yearly or more often since that time. She became pregnant soon after onset of her illness and carried the baby to term although there was rather persistent vomiting and albuminuria throughout the pregnancy. She was under medical care for some time afterward. Appendectomy was done the following year and diagnosis of chronic salpingitis and retroverted uterus was made. About four years later (1933) cystoscopy and urograms were done to investigate pyuria. Pus was obtained from both ureters, but the urinary tract films were negative. Guinea pigs inoculated with urine failed to develop tuberculosis. In 1941, at the age of 36, hyptertension was discovered; excessive menstrual flow developed and lasted for a year until hysterectomy was done. She became very weak and in the summer of 1942, began to suffer dyspnea even without exertion. Two months before admission, she began to have an unproductive cough and developed diarrhea and vomiting. Puffiness of the face, swelling of the abdomen and blurring of vision rapidly followed.

Past History: Tonsillitis at age 12 or 13 followed by tonsillectomy.

Physical Examination: T 37°, P 90, R 24, BP 192/110. Pale, dyspneic, tired and old-looking. Ocular fundi showed edematous discs and retinae with large exudates and arterial narrowing. There were basilar rales and diminution of breath sounds. The heart was enlarged to left, and the sounds were regular and forceful. A slightly tender liver edge was felt just below the costal margin. There was slight dependent edema. The venous pressure was 190 mm. and the circulation time (arm—tongue) 22 sec.

Laboratory: RBC 2.77 M, Hgb. 46 per cent, WBC 4,500 (P 82, L 16, M 1). Packed cell volume 24 per cent, Erythrocyte sedimentation rate 20 mm. Blood Wassermann negative. Plasma protein 6.4 gm. per cent. Timed urine (24 hrs.): sp. gr. 1.011, protein 1.1 gm., casts 600,000 (300,000 hyaline with fat droplets), WBC and epith. 159 M, RBC 6 M. Blood Urea 283 mg. per cent, creatinine 10.6 mg. per cent. *Electrocardiogram:* Left axis deviation and abnormal T waves. *X-rays:* Chest = enlarged heart, pulmonary congestion, left pleural fluid. Urinary tract = four small renal calculi on left, no definite enlargement of left kidney, right not visualized.

Course: The patient was digitalized and put on 40 gm. protein diet. Multiple small transfusions were given for about a month. There was a slight improvement in symptoms and the venous pressure fell gradually to 125 mm. and circulation time to 15 sec. The fluid in the chest increased though and the blood urea did not fall below 204 mg. per cent. The anemia progressed. Thereafter, the urea again rose, finally to 345 mg. per cent, and the patient died in coma 1/19/43 about two months after entry.

Dr. Arthur Selzer*: This 37-year-old woman presented evidence of cardiac and renal failure during her final illness. She gave a history of severe exertional dyspnea and dyspnea at rest, and had basilar rales, a tender, enlarged liver and anasarca as evidence of failure of both the left and right ventricle. This was confirmed by x-ray signs of pulmonary congestion, by prolonged circulation time and by increased venous pressure. In this case, where heart disease is not the only condition present, where in fact it appears the less important of the two conditions as it will be pointed out later, it is necessary to elaborate the presence of cardiac insufficiency more fully and emphasize the value of objective measurements. It is too often that we see the diagnosis of cardiac failure made without sufficient evidence, where symptoms and signs of it are actually due to something else, and occasionally the proper perspective of such a case is lost due to this misdiagnosis. It is well to remember that dyspnea may be due to intrapulmonary disease, or to severe anemia, and heavy breathing may be due to chemical stimulation of the center from diabetic acidosis or in terminal Bright's disease. Edema of the lower extremities is more often non-cardiac than cardiac and may be due to a number of causes, local, or general.

Applying all caution due to cases of renal failure, one is confident that this patient actually had heart failure by the appearance of the chest x-ray and the results of circulation time and venous pressure measurements. The question of structural etiological diagnosis of the cardiac lesion appears simple, as hypertension is the obvious factor. One may mention, in passing, other common types of heart disease, coronary heart disease occurring prematurely in hypertensives, rheumatic, congenital and luetic diseases, but there is nothing in this abstract to compel one to consider any of these conditions more seriously, especially in the absence of diagnosible valvular deformity, and with an electrocardiogram and x-ray apparently bearing out left ventricular strain and hypertrophy. It is of interest that digitalization of the patient resulted in improvement as recorded by objective measurements. One may guess that cardiac failure was a secondary factor in this patient's course for the patient died obviously a renal and not a cardiac death.

* Taken from the Clinical-Pathological Conference, San Francisco County Hospital, October 1, 1946.

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Coexistence of cardiac and renal failure is probably not as common as is generally believed. Renal insufficiency may imitate signs of cardiac failure, as it was pointed out, but it may also precipitate failure of a heart damaged by hypertension. Cardiac failure in this patient was due to this cause, and it is probable that the additional factor of the associated anemia, and possibly also due to changes in the composition of blood electrolytes were important factors. On the other hand circulatory changes associated with heart failure often cause transient nitrogen retention, but may also precipitate true renal insufficiency. It is very important to distinguish in this combination the primary and secondary factors from the prognostic standpoint, and in early cases from the therapeutic standpoint.

This patient's renal insufficiency is evidenced by the persistently high blood urea and correspondently high level of blood creatinine. One would like to have had determinations of calcium and phosphorus, as their reversed ratio confirms long-standing uremia and associated hyperplasia of the parathyroids. The diagnosis of renal disease is based on information gathered from the following procedures: history of previous renal disease; physical examination, examination of the urine; examination of the blood for retention of waste products; testing of the excretory function of the kidneys; visualization of the kidneys and urinary passages by radiography; and finally, by the presence or absence of hypertension.

The relationship of renal disease to hypertension is a subject where a great deal of confusion still exists. The initial enthusiasm which followed the experimental production of hypertension by clamping of the renal artery by Goldblatt has greatly subsided. It is generally accepted that the Goldblatt mechanism plays little part in essential, primary hypertension, which is the most common form of hypertension, for there is convincing evidence that hypertension may exist a long time with a normal renal blood flow and without structural changes in renal blood vessels, so that renal ischemia and vascular sclerosis are presumed to be the results and not the cause of hypertension in this group of cases. Hypertension may, however, develop secondarily to renal disease by a mechanism which may or may not be related to renal ischemia. Such a situation exists in the majority, though not in all forms of severe kidney disease, and the relationship is shown not only by the time of development of hypertension in renal disease but also by an occasional cure of hypertension after the removal of a diseased kidney.

In this patient, the association of renal disease and of severe hypertension—probably more severe than the blood pressure readings indicate, in view of severe hypertension retinopathy—suggest either primary hypertension in the malignant phase or the types of kidney diseases associated with hypertension, namely glomerulo-nephritis, pyelonephritis, polycystic kidneys, and periarteritis nodosa (and related vascular conditions). Other types of renal disease: tumors, tuberculosis, toxic nephrosis, amyloidosis, need not be discussed here for they seldom cause hypertension.

Essential hypertension is unlikely because of the recent onset of high blood pressure in the presence of a long history of renal disease and by the relatively low diastolic pressure, which usually persists even in failure. Glomerulonephritis cannot be completely ruled out, for it is known to exist in some cases in combination with urinary tract infection, but is not substantiated by any points in the patient's history nor by a pathognomonic urinary sediment. Polycystic kidneys, though compatible with intermittent kidney infection and late development of hypertension, are unlikely in the presence of a normal x-ray shadow of the kidneys and without palpable masses. Periarteritis nodosa may account for some odd clinical pictures but is not diagnosible unless a more distinctive clinical pattern is present.

Pyelonephritis is the one diagnosis which seems to fit best of all as the basis of this patient's course and terminal renal insufficiency. The history reveals repeated attacks of urinary tract infection since the age of 21 and a statement of the patient that pus was found in the urine recovered from the ureters. Granted that the urinary sediment is of little aid in diagnosis in the presence of uremia, the predominance of white and epithelial cells over casts in a quantitative study of timed urine favors somewhat pyelonephritis. Radiography shows shadows suggestive of renal calculi, but unfortunately no contrast visualization of the urinary tract was done so that there is no information available as to the renal pelves, nor can one know about the excretory status of the right kidney, which did not visualize in the ordinary film. If this last detail could be confirmed by a more reliable method, one could speculate about the possibility of a congenital malformation of the kidneys which so often is the basis of later infection. There is nothing definite in this abstract to favor such a possibility, especially since the patient made a statement that her kidney x-rays were normal ten years before her present illness. One can guess therefore that this patient had a long-standing urinary tract infection with repeated acute exacerbations, with extension and destruction of the kidney parenchyma and secondary, late hypertension resulting in cardiac hypertrophy and strain. The eventual outcome of this process was renal failure with uremia. Cardiac failure was secondary and of relatively less importance.

Dr. David A. Wood*: Dr. Selzer has presented a most clear clinical analysis of this case which is one of hypertension occurring as a sequel to an old bilateral pyelonephritis. Death was most probably on a uremic basis rather than that of cardiac failure. The parathyroid glands were considerably enlarged as a result of second-

* Associate Professor of Pathology, Stanford University School of Medicine.

ary hyperplasia, and one contained a small adenoma. Of interest was the presence of generalized arteriosclerosis which was unusually severe considering the fact that the patient was only 37 years of age. Excessive lipoid deposition in the involved vessels as well as the presence of a collection of "xanthoma cells" in the wall of an artery in the spleen suggested the possibility of a concurrent generalized disturbance in lipoid metabolism.

The autopsy revealed a marked pitting edema of both lower extremities which extended to the knees. Large amounts of clear fluid were present in the serous membrane cavities. In the peritoneal cavity 800 cc. were found; in the left plueral space, 800 cc., and in the right, 700 cc. Present in the pericardial sac were 500 cc. of thin fluid which was slightly blood tinged, and bounded by slightly roughened hyperemic surfaces.

Both kidneys were markedly shrunken with slightly thickened adherent capsules. They weighed 60 grams each. Their surfaces were irregular, scarred and pitted. Some of the scars were flat and depressed. Small, intervening cortical cysts were scattered throughout and measured up to a maximum of 0.5 cm. except for one cyst in the right kidney which measured 1.5 cm. in width. Upon cut section the cortex of each kidney was found to be irregularly thin. The pelvis of each kidney appeared large and the calyces dilated. This was more apparent than real, however, due to the marked loss of renal substance. No obstruction or calculus was found in either pelvis or ureter. (The autopsy failed to account for the four calcified shadows demonstrated radiologically in the left flank.) Except for the right renal pelvis the lining mucosa was pale and intact. The mucosa of the right pelvis revealed hyperemic areas and several white flat plaques. Several similar white plaques were found in the mucosa of the urinary bladder, whose lumen contained 50 cc. of blood tinged urine, and whose wall was quite thickened and rubbery. There were no aberrant renal arteries or unusual fibrous bands about the hilus of either kidney.

Careful inspection of each renal artery revealed no obstructing intimal plaques of significance.

The heart was enlarged at least one and a half times normal size and weighed 470 gm. Its pericardium showed a recent pericarditis which was interpreted as occurring most probably on an uremic basis. There was a moderate concentric hypertrophy of the left ventricle whose wall was thickened and measured up to a maximum of 1.5 cm. No scars were grossly evident in the myocardium. There was no thickening of the right ventricular wall and no dilatation of the chambers on the right side. The ostia of the coronary arteries were patent although their lumina were encroached upon considerably by athermatous plaques in the intima of the aorta.

Both lungs were aerated and except for a small amount of hypostatic edema revealed no significant findings. The left lung weighed 290 gm., and the right 440 gm. Chronic passive hyperemia was not grossly evident.

Two parathyroid glands had a combined weight of 0.3 gm. One contained an oval adenoma occupying about one-third of the total bulk of the gland.

Numerous atheromatous intimal plaques were distributed throughout the course of the aorta and into the branches of the celiac axis. As previously stated, the main renal arteries were relatively free of intimal thickening.

The abdominal viscera showed no chronic passive hyperemia. The liver weighed 1,440 gm., and the spleen 170 gm. Neither revealed grossly significant changes.

Bacteriologically, blood from the heart revealed no growth after seven days. Smears from the renal pelvis showed many gram-positive cocci in pairs or in short chains. In histological sections of the heart very occasional cocci were demonstrated in the pericardium.

Study of the microscopic sections confirmed the gross diagnosis of old, bilateral pyelonephritis. Sections of the kidneys showed numerous lymphocytes in the submucosa of the renal pelvis. Occasional small groups of lymphocytes were scattered throughout the cortex and medulla. This was associated with an irregular fibrous thickening of the interstitial tissue. Glomeruli were few in number and several of those which remained showed varying degrees of hyalinization. No crescents, or adhesions between the tufts and Bowman's capsules were found, such as one might have expected in a chronic hemorrhagic Bright's disease. Quite uniformly, the medium-sized arteries and arterioles showed extensive changes. The former showed much concentric fibroblastic intimal thickening, and the latter much subendothelial accumulation of hemogenous hyaline-like material, resulting in marked narrowing of the respective lumina. Extensive but less severe arteriolar changes were also noted in the spleen, pancreas, and adrenal. One artery in the spleen showed a subtotal obliteration of its lumen by loose intimal tissue containing many "xanthoma cells."

The parathyroid glands showed a marked hyperplasia of chief cells resulting in a compressed stroma and a compact structure. Occasional clumps of oxyphil cells remained, and in places there were occasional cells with water clear cytoplasm (wasserhelle cells). One gland contained an oval adenoma which consisted of chief cells whose nuclei were more deeply staining and whose cytoplasm was less abundant.

Sections of the heart showed a shaggy layer of fibrin covering the epicardium. Immediately beneath this a narrow sub-epicardial zone was infiltrated by moderate numbers of lymphocytes. Bacterial stains revealed occasional pairs of lancet shaped cocci and several clusters of small round cocci.

In summary, this is a case of old, bilateral pyelonephritis. It seems quite evident that the hypertension in this case occurred as a sequel to the pyelonephritis. The absence of athermomatous involvement of either main renal artery is worthy of note. Occasionally, the presence of a large intimal plaque in one of the renal arteries may possibly result in sufficient ischemia of the kidney as to result in the development of hypertension. There is no evidence of glomerulonephritis. It seems quite clear that pyelonephritis constitutes the essential lesion. Arteriolar lesions in other organs (pancreas, spleen, and adrenals) are most probably secondary to the hypertension. As was to have been expected in such a long standing case of pyelonephritis, the parathyroid glands showed a notable secondary hyperplasia. Normally, the upper limits of normal for the combined weight of all four parathyroid glands is not in excess of 150 mg.; yet, in this case the weight of only two glands was 300 mg. Whether the small adenoma is a part of this hyperplasia or represents a separate process is impossible to determine. No bone changes of hyperparathyroidism were demonstrated.

The absence of significant chronic passive congestion in the lungs and viscera as well as the absence of notable dilatation of the heart suggests that heart failure did not constitute the principle cause of death. It is likely that the latter was most probably uremic. Not only were the values for blood urea high during the last two months of this patient's life, the last recorded determination being 345 mg. per cent, but a rather typical sero-fibrinous pericarditis was found.

Student: What is the significance of the pericarditis?

Dr. Wood: Terminally, uremia not uncommonly is associated with the development of fibrinous pericarditis. Usually, not so much fluid is present as was found in this case. Ordinarily, it is a "sterile" pericarditis, inasmuch as the pathologist is usually unable to demonstrate organisms. The fundamental reason for its occurrence with uremia is not well understood.

CHILDREN BORN WITH SYPHILIS RESPOND WELL TO PENICILLIN TREATMENT

In a study of 61 children, two Atlanta physicians have found that penicillin is effective in the treatment of congenital syphilis.

Mrs. Joseph Yampolsky and Albert Heyman, who are from the Department of Pediatrics and Medicine of Grady Memorial Hospital and Emory University School of Medicine in Atlanta, used penicillin to treat the 61 syphilitic children, according to the October 19 issue of *The Journal of the American Medical Association.*

Thirty-two of the 61 children had simple infantile congenital syphilis. Twenty-three of the 32 responded satisfactorily under the penicillin treatment. "All 23 are clinically well, have normal spinal fluids and exhibit no clinical evidence of the disease," the authors say.

While three of the patients died, the authors believe that the fatalities were in no way related to the treatment. Two of the deaths "apparently resulted from an overwhelming syphilitic infection in premature and malnourished infants, while the third fatality remains unexplained."

In discussing the remaining 29 patients, the Atlanta doctors say that seven were suffering from acquired primary and secondary syphilis, while the others were treated for late forms of congenital syphilis.

In the seven cases of acquired syphilis, the doctors say the patients were treated with doses of penicillin comparable to those used in adults. "The syphilitic lesions healed promptly in every case and the spirochetes disappeared rapidly," *The Journal* article says, adding: "All of these children have been followed for at least six months.

"The results obtained with penicillin in the treatment of syphilis in children seem to depend on the nature and duration of the disease. Although penicillin appears to be effective in the treatment of infantile congenital syphilis and in early neurosyphilis, little or no response can be expected in the treatment of the late manifestations of this disease."

Mrs. Yampolsky and Heyman say that while the optimum dosage of penicillin cannot be determined in such a small series of cases, "we believe that a total dose of penicillin of 100 000 units per kilogram of body weight is effective in the treatment of the majority of these cases."

CLINICAL CONFERENCE

Macrocytic Anemia With Edema

FROM THE COLLEGE OF MEDICAL EVANGELISTS, LOS ANGELES

DR. OLOV A. BLOMQUIST*: The patient presented today is interesting both from the diagnostic and therapeutic viewpoints. She is a 58-year-old white housewife who first entered the White Memorial Hospital on July 5, 1940. At that time she complained of swelling of the hands, legs and feet; orthopnea, cough, and vomiting spells. These symptoms had been present for two months. Difficulty in walking due to weakness, and numbness of the feet had been present for three weeks.

Two months before admission she first noted swelling of her hands and legs which became steadily worse until it involved the entire legs and thighs. At the same time oliguria and generalized pruitis developed. Dyspnea on slight exertion, a non-productive cough, palpitation, throbbing in her head, nausea and vomiting had also been present for two months. The nausea and vomiting occurred irregularly and were not related to meals but did result in a marked decrease in food intake. Friends told her that she had begun to look very pale two months before admission.

Physical examination revealed a 52-year-old white female who was obese, very pale and who presented generalized edema which was most marked in the dependent portions of the body, but which was also present over the arms and the shoulders. The temperature was 36.7°, pulse 88 per minute, respiration 22 per minute, and blood pressure 125/65 mm. Hg. The sclerae showed an icteric tinge but the eyes were otherwise normal. The ears, nose, and mouth were normal. The tongue was not atrophic or beefy. There was marked pulsation of the deep jugular veins. The apex of the heart was 12 cm. from the mid-sternal line in the left fifth intercostal space; the rhythm was regular; P_2 was accentuated and reduplicated; a blowing systolic murmur was heard over the entire precordium, best at the apex. The lungs were normal on physical examination. Due to the marked edema examination of the abdomen was difficult but there was fullness in the right upper quadrant suggestive of an enlarged liver. The legs and thighs were markedly edematous.

On admission the urine showed a specific gravity of 1.014 and a trace of albumin but was otherwise normal. Hematologic examination showed 1,000,000 erythrocytes per cubic mm., 4.2 gm. hemoglobin (25 per cent of 17 gm.), color index 1.25, 4,150 leucocytes per cubic mm., polymorphonuclears 68 per cent, eosinophiles 4 per cent and lymphocytes 28 per cent. There was anisocytosis 3 plus, poikilocytosis 2 plus and polychromatophilia 2 plus. The platelet count was 36,000 per cubic mm. The reticulocyte count was 1.5 per cent. Numerous Howell-Jolly bodies were present and a few normoblasts were seen. Sternal marrow showed 5 per cent megaloblasts. Blood Wassermann was negative. Serum albumin was 3.6 gm. and globulin 1.5 gm. per 100 cc. of serum. The icterus index was 13. Urea clearance was 88 per cent of normal in the first hour and 71 per cent of normal in the second hour. Fractional gastric analysis with histamine revealed no free hydrochloric acid.

The electrocardiogram showed low voltage in the three standard leads with a maximum QRS deflection of 0.5 mv.

An orthocardiogram revealed generalized cardiac enlargement; both ventricles, both atria and the pulmonary conus were prominent. The cardiothoracic ratio was 17.5/27. There was considerable hilar congestion and a small amount of fluid at both bases of the lungs.

Gastrointestinal x-ray series was entirely normal.

The patient was placed on a high protein, low salt (2 gm. daily) diet. She was given two cc. of liver extract intramuscularly daily (approximately 30 u. daily, but in 1940 liver extract was not standardized by units so the unitage is an approximate figure). She was given 500 cc. of whole blood. All other treatment was withheld, except for general nursing care and simple sedation.

The reticulocyte response was 2.6 per cent on July 21, 1940, 9.3 per cent on July 23, 15 per cent on July 24, and 6 per cent on July 28.

On July 28, 1940 the blood showed 2,990,000 erythrocytes per cubic mm., hemoglobin 11 gm. (63 per cent of 17 gm.) and the color index was 1.1. The total leucocyte count was 5,650 per cubic mm. and the differential count was about the same as on admission.

By July 18 (approximately two weeks after admission) she was feeling a little better and her orthopnea and cough were less annoying. By July 21 the urinary output exceeded the fluid intake and this continued throughout her hospital stay. The edema decreased slowly but steadily until she went home on August 25, 1940, with no clinical evidence of edema.

At the time of discharge her blood showed 4,270,000 erythrocytes per cubic mm., hemoglobin 14.2 gm., color index .97, total leucocyte count 5,700 per cubic mm. with 53 per cent polymorphonuclears, 7 per cent eosinophiles, 32 per cent lymphocytes and 8 per cent monocytes. The cardio-thoracic index was 13.4/27. The voltage of the QRS complexes on the electrocardio-

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gram showed a marked increase over the previous tracing to 1 millivolt or a little more. The lungs were clear and free pleural fluid had disappeared.

This patient has been followed as an outpatient for the past six years. Since her discharge from the hospital she has continued to take liver extract regularly and has remained well ever since. She has had no symptoms of cardio-vascular disease, no edema, no anemia and no gastrointestinal distress.

DR. RAYMOND M. HILL**: In considering this problem we must answer two questions. What is the mechanism of the anasarca? What type of anemia is this?

Edema of this extent may be due either to disturbance of the extra cellular fluid osmotic relationships, increase in the hydrostatic venous pressure, or a combination of the two.

Associated contributory factors in the production of generalized edema include: (1) Capillary anoxia with increased permeability of the capillary bed, (2) decreased excretion of the sodium ion (as seen with excessive administration of desoxycorticosterones), or (3) increased dietary intake of the sodium ion as sodium chloride, or sodium bicarbonate.

There is considerable evidence in favor of disturbed extracellular fluid osmotic relationship in this case, although the cause of the decreased plasma proteins which were reported as 4.7 and 5.0 grams per 100 cc. of plasma, is not too evident. She did not have enough albuminuria to produce the decrease in plasma proteins. There is insufficient evidence to say that the decreased plasma protein is due to inadequate dietary protein intake.

I would hazard a guess that the decreased plasma proteins were due to a combination of decreased dietary protein intake, inadequate production of plasma proteins in the liver due to the severe anemia, loss of plasma into the extracellular tissues, and possibly a dilution factor associated with an increased plasma volume.

The normal osmotic pressure of blood is approximately 28 mm. Hg. One gram per cent of albumin increases the osmotic pressure approximately 5.5 mm. Hg., and 1 gram per cent of globulin increases it 1.9 mm. Hg. Based on such figures this patient had a plasma osmotic pressure of 21 or 22 mm. Hg. Hence all of the edema could be explained on an osmotic basis.

The anemia, leukopenia, thrombocytopenia, increased color index, increased volume index, and the megaloblasts in the sternal marrow are characteristic of macrocytic anemia. It is more difficult to determine whether it is a nutritional macrocytic anemia, or pernicious anemia. Megaloblasts in the sternal marrow have been considered pathognomonic of pernicious anemia, but they are also found in nutritional macrocytic hyperchromic anemia. A diagnosis of pernicious anemia should not be made if there is free hydrochloric acid in the stomach contents, but achlorhydria does not exclude the diagnosis of nutritional macrocytic anemia.

The anemia, because of resulting capillary anoxia could have produced increased permeability of the capillary bed, and therefore edema. The increased capillary permeability would allow the albumin to escape from the plasma into the extracellular tissue spaces which would result in a decreased plasma protein level. I will not discuss the problem of the so-called heart of anemia.

I am debating whether to conclude that she had nutritional disease associated with hypoproteinemia, macrocytic hyperchromic anemia, vitamin B deficiency and congestive heart failure, or pernicious anemia with congestive heart failure and peripheral neuritis. The dramatic clinical response to liver extract, in my opinion, establishes the diagnosis of pernicious anemia with congestive heart failure.

DR. HAROLD J. HOXIE†: Generalized edema that is not of inflammatory or allergic origin has a tendency to be more in the dependent parts, regardless of the principal factors in causing the edema. Inflammatory edemas such as that of glomerular nephritis are determined by passage of sufficient protein through abnormally permeable capillaries so that water is held in the tissues, usually the looser tissues, in defiance of gravity. In practically all other types of general edema the hydrostatic pressure within the blood vessels is enough of a factor so that the edema is affected by dependency. This effect is more or less proportional to the importance of the intravascular hydrostatic pressure factor in the edema.

It is rare to find a patient with general edema in whom the edema can be attributed to disturbance of only one of factors that control interchange of body fluid between capillaries and tissue space. This patient had several factors conducive to edema. Distended veins in the neck indicate increased pressure transmitted back to the capillaries. Arteriolar dilatation as a part of the compensation for severe anemia tends to expose the capillaries to more of the pressure originating in cardiac systole. Both these factors tend to increase the filtering pressure in the capillaries. The tissue pressure outside the vessels resisting edema formation may have been reduced by loss of flesh during three months of illness.

The reduction of both albumin and globulin in the serum is another factor conducive to edema. Both fractions of serum protein were reduced to about the same extent indicating dilution and lack of production to be the chief factors rather than the albuminuria. The low globulin value tends to eliminate portal cirrhosis as a cause of the anemia.

We sometimes are able to eliminate edema by treating one of the edema producing factors. We cannot conclude that this is the only causative factor because in most patients edema results from a summation of factors.

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This patient's case illustrates the interdependence of the various bodily systems. The cardiovascular system, the kidneys, the adrenal cortex, the digestive system, the respiratory system all had their functions disturbed by failure of the hemopoetic system to produce enough red cells.

DR. WILLIAM PAUL THOMPSON*: It appears that there is sufficient evidence to support the contention that heart failure played a part in the genesis of the symptoms and physical findings. The heart was large, the venous pressure was elevated, and congestion was present in lungs, liver and subcutaneous tissues. The disappearance of these abnormalities with disappearance of the anemia establishes beyond reasonable doubt that this is an example of the so-called heart of anemia, one of the reversible forms of heart disease.

DR. WALTER E. MACPHERSON**: Surely this is a very interesting case. The fact that the patient is now well and free from symptoms is of primary importance to her and makes us feel good.

The discussion, however, has been most valuable in diverting our attention and thoughts to the underlying disturbances in physiology. The fact that the patient has a primary hyperchromic macrocytic anemia seems to be well supported. The clinician who supervised her treatment took special precautions to change her previous program in only one important respect, namely, the use of liver extract.

Therefore, it seems reasonable to conclude that the chief factor which was responsible for initiating the various disturbances in physiology which accounted for her findings and symptoms was the anemia.

In trying to reconstruct this picture one has a right to assume that there was sufficient anoxia to cause a moderate degree of heart failure, to cause an increase in capillary permeability, and to cause a moderate decrease in liver function, particularly in the formation of serum protein.

I agree with Dr. Hill that the fact that this is rather an unusual picture for this type of anemia strongly suggests an underlying nutritional deficiency which by itself was relatively benign. At any rate, it appears as though a vicious cycle, the component parts of which were moderate myocardial failure, increased capillary permeability, and decreased liver function, with each one contributing to the disturbed function of the other, could well explain the clinical picture which is presented. The fact that the elimination of the anemia was sufficient to break up this vicious cycle is of interest. From all reports which are now available, one assumes that the general physiology of the patient is reasonably well within normal limits.

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MILLIONS WASTED ANNUALLY ON HOME REMEDIES FOR COLDS, GRIP

Outmoded self-treatment methods and commercial advertising are largely responsible for the waste of millions of dollars annually by people with colds, grip and influenza, according to Hobart A. Reimann, M.D., of Philadelphia.

Writing in the November 2 issue of *The Journal of the American Medical Association*, Dr. Reimann, of the Jefferson Medical College and Hospital, refers to many of the preventive and therapeutic measures in common use as "obsolete" and "illogical." He especially condemns the waste of the sulfonamide compounds and such antibodies as penicillin which are ineffective for these viral infections.

Respiratory diseases are widely prevalent and "account for most of the home visits (32 per cent) and provide the second most common reason (15 per cent) for office visits to general practitioners," states the author. "The average person is said to suffer from one to four bouts each year, accounting for about 250,000,000 infections annually in the United States. Infections of the respiratory tract cause more loss of time from industry and from schools than all other diseases combined. They are rarely a direct cause of death, but they precede or incite many other serious infections [such as pneumonia or meningitis]."

Except for influenza vaccine there are no specific preventive procedures, and no specific treatment exists for any infection of the group. The most that can be done for the patient is to relieve discomfort, to prevent complications without impeding the natural process of recovery and to minimize the spread of infection to others.

If aching and headache are present they are best controlled by warmth, rest in bed and the use of an analgesic. There is no need to change from the normal diet and fluid intake in the average infection. Rest, as for any other infectious condition, is the best treatment for it serves several purposes: (a) aids recuperation, (b) lessens complications, (c) prevents the spread of the disease to others and (d) keeps the patient from acquiring a more serious infection from contact with "carriers."

Good health alone is no insurance against colds. Dr. Reimann points out that "although excellent physical condition, peace of mind, adequate diet and pleasant weather supposedly furnish resistance, infections of the respiratory tract occur for no obvious reason in otherwise robust persons. However, certain circumstances known by common experience to lead to colds such as exposure to wet and cold, sudden chilling in drafts, volatile irritants, dust, fatigue and other excesses should be guarded against, or neutralized by rest, warmth and comfort. Reasonably comfortable temperature and humidity of air in rooms is desirable, but no evidence is available as yet of their specific value. Residence in a climate where colds are less frequent is recommended for those who are subject to frequent infections, if economic circumstances permit."

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NOTICES AND REPORTS

C.M.A. Radio Show Has Audience of 600,000

Every Saturday evening, from 9:15 to 9:30, more than 600 000 people in California tune in the California Medical Association radio program, "California Caravan," aired over 18 stations in the Mutual-Don Lee Broadcasting System. They not only hear a good show, but also hear about California Physicians' Service and the advantages of pre-paid medical care.

Inaugurated June 15 by The Council of C.M.A. as a new phase of California medicine's public relations program, "California Caravan" established its popularity with the vast radio audience within a month, according to Hooperating, the standard survey service of the radio industry.

The Hooperating of the C.M.A. program for July, 4.8, indicates an average audience of 635,000 listeners per show and is a better rating than that given many of the big-budget and big-name shows for that period.

Here are some comparative ratings compiled from the July telephone survey of radio audiences conducted by C. E. Hooper, Inc., showing the relative standing of C.M.A.'s program:

"Can You Top That?"	6.6
"Ford Program"	2.1
"Standard Hour"	8.6
"Orson Welles' Mercury Theater"	3.7
Nash Kelvinator	4.3
"Theater of Romance" (Colgate)	4.2
Fred Waring (Johnson Wax)	4.5
"CALIFORNIA CARAVAN," C.M.A. program	4.8

The stimulus of C.M.A.'s public relations program in building California Physicians' Service—through newspaper and radio advertising, publicity and the campaign of "Voluntary Health Insurance Weeks," which has now covered 25 counties—is indicated by the fact that C.P.S. enrollment has doubled since January 1 of this year—and every person enrolled in a voluntary health system in California is building stronger the medical bulwark against COMPULSORY health insurance.

C.P.S.—Growth and Problems

Although a doubling of the enrollment of beneficiary members of California Physicians' Service in the first ten months of this year has been attended by a higher average cost per claim and a necessary increase in membership dues, an outstandingly hopeful development is seen in the type of group now being enrolled.

The board of trustees looks upon the recent enrollment of the members of the Merchants and Manufacturers Association in Southern California as indication that managerial, as well as employee groups, are giving recognition to the value of C.P.S. Moreover, it is felt that this trade association of some 1 500 business organizations offers a large potential of further new membership. The same is true of the Lettuce Growers' Association of Salinas Valley, which has recommended that C.P.S. be considered by all its members.

Among other large groups recently enrolled are the May Company of Los Angeles, Bordens Dairy, the San Bernardino Air Base and the Southern California Telephone Company. An interesting departure is the current enrollment of employees at Hunters' Point Naval Base.

Enrollment of members of chapters of the California State Grange has proceeded apace. To date over 10 000 people in 175 chapters have been enrolled under a surgical and hospital coverage plan which C.P.S. submitted last spring at the request of the State Grange.

Negotiations are still under way with the Standard Oil Company of California, which had requested a program of medical, surgical and hospital care for dependents of its employees. Due to unforeseen difficulties, enrollment there has not yet begun. The Southern Pacific Railroad and the Pacific Electric Company of Los Angeles are now studying proposals for care of dependents of their employees which C.P.S. submitted at their request.

Inevitably, increased membership has brought with it additional administrative problems for C.P.S. There has been a very heavy increase in utilization of service. The average cost per claim has risen from $17 to $24. Statistics show that groups in existence less than four months are accounting for 40 per cent of total claims. Groups with membership of a year or less are using 60 per cent of the total.

RATE INCREASE

As was reported at the May meeting of Administrative Members, in October, 1945, the total deficit was $279,144.21. By May 1, 1946, this had been reduced to $137,912.66. Due to the large number of surgical contracts which make up the beneficiary membership, C.P.S. experienced, during the summer months, a very heavy utilization of service. Because of this, reduction of the deficit has not been as rapid as was anticipated.

At the Board of Trustees meeting held August 11, 1946, the Board, upon advice from the administration, voted an increase of dues to beneficiary members in the amount of approximately 25 per cent. The increase is being put into effect as rapidly as possible.

The necessity for a rate boost is not out of line with the experience of other medical care plans throughout the nation—Blue Cross hospital plans among them—which have had to put increases into effect as costs have mounted in the general inflationary trend.

The number of beneficiary members, which had increased by 81,350 to a total of 208,192 during the 12 months preceding the annual meeting of C.P.S. Administrative Members held in May of this year, more recently has been rising at an accelerated rate. As of November 1, the total was 327,481, almost double the 170,000 on the books at the beginning of the year. The increased rate of growth is particularly gratifying to the trustees because it has been accomplished during a period when rapid turnover of employees in many industries and services has presented difficulties to enrollment.

VETERANS' PROGRAM

Membership figures of course do not include the beneficiaries under the C.P.S. arrangement with the Veterans' Administration for medical care of veterans of the armed forces. Reports from the field are that this program is running smoothly. An indication of the size of this program is contained in a recent figure showing that there are now 1,400,000 veterans in California. In August, $175,694 of Veterans' Administration funds was earmarked to pay physicians for services to veterans, and there is a considerable increase with each succeeding month.

Beyond immediate aspects, the medical care plan for veterans is redounding in good will for C.P.S. Colonel J. C. Harding, Chief of the Veterans' Administration Out-Patient Department and assistant to General Paul R. Hawley in Washington, on a recent visit to California Physicians' Service offices in San Francisco said that C.P.S. had the best such program in the United States. Further recognition of the California program came in the form of a visit from a member of the Wisconsin Veterans' Program, who was sent to study procedures under the plan in California. As a result the Wisconsin organization is modeling a veterans' program after the California plan.

EXPLANATION PROGRAM FOR PHYSICIANS

Expanding beneficiary membership and the growing use of the veterans' care contract have brought with them a need for a more active program of explanation for the physician members, who now number more than 7,500. To this end, the C.P.S. medical director and assistant medical director, together with representatives from the department of professional relations, have arranged speaking dates with all County Medical Societies to present information on the workings of both the Commercial and the Veterans' Programs. Response to the meetings held thus far has been excellent and demonstrative of interest by the profession as a whole. Question periods which are a part of the meetings have developed added information of value not only to member physicians but to the management of C.P.S. as well.

The growing volume of business has dictated expansion in the organization and additions to personnel of C.P.S. There are now 19 district offices, including one in Sacramento County, in addition to the Los Angeles and San Francisco general offices. C.P.S. now has 245 full-time employees, 72 of whom are employed jointly with Blue Cross in Southern California. The Veterans' Program alone now requires 58 employees.

In the expansion in membership—particularly in the character of recent enrollments—in the smooth operation of the Veterans' Program, and in the growing recognition accorded C.P.S., the management sees encouragement for an expanding program of medical care on a voluntary prepaid basis.

CHESTER L. COOLEY, M.D., *Secretary.*

Information for Authors, Participants in Symposia and Panel Discussants

1. All members taking part in such programs should have a manuscript ready for presentation to the Section Secretary. The manuscript does not need to be followed verbatim at the meeting itself, but must be available for consideration by the Editor of CALIFORNIA MEDICINE for publication in that Journal.

2. All manuscripts become the property of the California Medical Association until officially released, upon written request of the author, for publication elsewhere.

3. Members are reminded that each lantern slide takes approximately one minute for presentation and that no lantern slides should have more than about six lines of text on them. Lantern slides containing voluminous chart or statistical data are largely a waste of time. The interest of the audience is better held by succinct presentation of the principal points.

4. Authors must inform Section Secretaries in advance of any special equipment needed for presentation of papers, other than standard lantern slides (3¼" x 4" glass slides).

5. Extra time is not allowed for the presentation of slides, movies or other material, however remarkable, except by arrangement at least three months before the annual meeting.

6. Authors submitting pictures or charts for use with their articles when published are reminded of the rule limiting to $15 the amount which CALIFORNIA MEDICINE may spend for engravings to reproduce illustrations. (Fifteen dollars will buy approximately a half page of engravings for shaded drawings or photographs and three-quarters of a page of absolute black and white engravings.) When an author wishes to include more engravings than can be paid for by CALIFORNIA MEDICINE under the $15 limitation, the usual practice is to bill him for the amount by which the cost of engravings exceeds the limit.

7. References listed at the end of manuscripts submitted for publication in CALIFORNIA MEDICINE should follow the style used in the Quarterly Cumulative Index Medicus—the author's name first, followed by the title of the article, then the name of the publication abbreviated as it is in the Cumulative Index, the volume number, page number, month of issue (with the day of the month if the journal listed is published oftener than monthly) and the year. Example: Fox, C. L., Jr.: Oral Sodium Lactate in Treatment of Burn Shock, J.A.M.A., 124:207 (Jan. 22), 1944.

When reference is made to a book, the order should be: Author's name, title of book, name and address of the publisher, and the year of publication.

Lists of references should be arranged alphabetically by author's name, so that the reader on seeing a name in the text may turn to the bibliography and find the full reference in the alphabetical listing.

Information for Section Secretaries

The following information is for the guidance of Section Officers in connection with Annual Meeting of the California Medical Association.

1. All papers read at the Annual Meeting must be ready for handing to the Section Secretary at that meeting.

2. Speakers should be urged to prepare a condensed version of their papers for "verbal" presentation (in addition to the regular copy for submission to the Section Secretary for the editor of CALIFORNIA MEDICINE.)

3. All papers must be preceded by an abstract not to exceed 50 words, mailed to the Association office, 450 Sutter Street, San Francisco, by February 1.

4. Papers should be designed for presentation in 15 minutes; the maximum time allowed is 20 minutes. The Section Chairmen should signal speakers at the end of 17 minutes, to indicate that only 3 minutes remains.

5. Discussions should ordinarily be limited to 5 minutes; no person may speak twice on a subject except by permission of the meeting; the authors' closing discussions are limited to 5 minutes.

6. Section Chairmen are requested to notify speakers when their time is reached.

7. Under special circumstances (distinguished authorities, specially invited discussants, members of symposia, etc.) a speaker or discussant may be allocated times longer than the above. This must be done by prearrangement, with the allotted time indicated in the program.

8. All papers read at the Annual Meeting are accepted on the condition that they are contributed solely to CALIFORNIA MEDICINE; members desiring to publish their papers elsewhere must make written application to the Editor.

9. A member may not present a paper in each of two succeeding years, or more than one paper at each session. Failure of a member to comply with these rules precludes acceptance of further papers for a period of two years.

10. Section Secretaries *must* inform the Committee on Scientific Work in advance of any special equipment needed for speakers, other than standard size lantern slide projector and screen.

In Memoriam

Conlan, Peter Timothy. Died at Los Angeles, July 15, 1946, age 75. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1898. Licensed in California in 1927. Doctor Conlon was a Retired Member of the Los Angeles County Medical Association, and of the California Medical Association.

✤

Gasteiger, Ernest Sipe. Died at Sawtelle, September 14, 1946, age 46. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1927. Licensed in California in 1928. Doctor Gasteiger was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

Joesting, Harold Carl. Died at Los Angeles, September 18, 1946, age 42. Graduate of the University of Minnesota Medical School, Minneapolis, Minnesota, 1929. Licensed in California in 1942. Doctor Joesting was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

Maroon, John Luther. Died at Santa Ana, October 9, 1946, age 72. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1912. Licensed in California in 1917. Doctor Maroon was a member of the Orange County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

Picard, William J. Died at Berkeley, September 30, 1946, age 59. Graduate of Albert-Ludwigs-Universität, Medizinische, Fakultät, Freiburg, Baden, 1917. Licensed in California in 1939. Doctor Picard was a member of the Alameda County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

Schaefer, Anton Henry. Died at Berkeley, September, 29, 1946, age 41. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1941. Licensed in California in 1941. Doctor Schaeffer was a member of the Alameda County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

Swauger, Luella Stone. Died at Oakland, September 16, 1946, age 75. Graduate of California Eclectic Medical College, Los Angeles, 1892. Licensed in California in 1893. Doctor Swauger was a member of the Alameda County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

Claud E. Norris. Died August 31, 1946, age 67 years, of carcinoma of the lungs. He was a graduate of the St. Louis Medical School. In 1910 he connected with the Philippine Island health service and served in various parts of the islands, eventually becoming senior health officer there. In 1923 he returned to the United States and entered the Tulane University Medical School. He then took up private practice in Eureka, California. He leaves a wife, Sadie B. Norris, and a brother, Dr. Clarance O. Norris.

NEWS and NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Return of four Alameda County physicians from service in the armed forces to private practice is announced in the October issue of the Bulletin of the Alameda County Medical Association. They are **John Blum,** internal medicine, 2140 Shattuck Avenue, Berkeley; **Lynn Foree,** general practice and surgery, 379 30th Street, Oakland; **Harrel Lee Harrington,** urology, 379 30th Street, Oakland; **Henry S. Patton,** plastic and reconstruction surgery, 411 30th Street, Oakland.

COLUSA

The Colusa County Board of Supervisors has appointed **Dr. E. Sturgis Bramlett,** Colusa physician and surgeon, as county health officer for a term of one year. Dr. Bramlett will assist **Dr. J. E. Tillotson,** who remains as county physician and medical director of Colusa Memorial and Colusa County Hospitals. As County Health Officer, Dr. Bramlett succeeds **Dr. Charles F. Keith** of Williams, who resigned, effective October 1.

FRESNO

Dr. Samuel Ross, recently released from the Army with the rank of lieutenant-colonel, has resumed his practice in Fresno, with offices in the Fulton-Fresno building. Dr. Ross has just completed postgraduate work in clinical allergies in the graduate school of the University of Southern California.

LOS ANGELES

German physicians, cut off from medical advances in the western world for five years, will be **re-educated in modern techniques** in a program directed by **Dr. E. Ross Jenney** of Los Angeles, chief of the Public Health Branch of the Office of Military Government for Bavaria, the office announced. Dr. Jenney, formerly a colonel in the Army Medical Corps, was sent to Europe in 1944 where he was awarded a citation by King Haakon VII for distinguished services while with the public health division of the Allied Mission to Norway.

Having recently returned from military service, **Dr. Allan B. Wilkinson** has opened an office for the practice of general surgery at 136 North Central Avenue, Glendale.

Dr. Frank R. Anderson, physician and surgeon, has opened a new office at 71 North Baldwin, **Sierra Madre.** Dr. Anderson served with the United States Navy Medical Corps during the war. Before that he practiced medicine in San Jose for approximately 15 years.

Dr. Maxwell Andler, resident physician of Los Angeles General Hospital, has been elected president of the hospital's Interne Residents' Association. Other officers chosen are **Dr. John Armstrong,** vice-president; **Dr. John Zaro,** treasurer; **Dr. Laurel Weibel,** secretary. Dr. Andler succeeds **Dr. William Grube.**

Dr. Grover Kempf last month took over his new position as chief of the United States Public Health Service, with jurisdiction over incoming vessels and planes from San Luis Obispo to San Diego. **Dr. Kempf** will make his headquarters at the Terminal Island quarantine station. He succeeds **Dr. R. H. Heterick,** 65, who retired after 38 years in the service.

RIVERSIDE

Dr. C. H. Baldwin, formerly of New Hampshire, is now associated with **Dr. Charles H. Peppers** and **Dr. W. P. Aiken** at 483 North Palm Canyon Drive, Palm Springs.

SACRAMENTO

At a testimonial dinner held recently at the Sutter Club in Sacramento, **Dr. Andrew M. Henderson** was honored on the occasion of his retirement as Sacramento Division surgeon for the Southern Pacific Company. The dinner was attended by Southern Pacific officials from San Francisco and Sacramento and a number of Sacramento physicians. Dr. Henderson joined the S.P. in 1893, left for further study in Europe and the East, and returned in 1906.

Governor Warren has announced the appointment of **Dr. William F. Quinn** of Los Angeles to the State Board of Medical Examiners for the term ending January 15, 1950. Dr. Quinn, a member of the department of surgery at the College of Medical Evangelists, succeeds **Dr. George Thomason,** whose term expired.

SAN DIEGO

Dr. S. J. McClendon, president of the California Medical Association, recently returned from Rio de Janeiro where he was invited to present a paper on Rheumatic Fever at the first Inter-American Medical Congress. At the conclusion of the meeting he was **elected to the board of directors** for the next congress, scheduled for 1948 in Mexico City. The congress was organized under auspices of the National Academy of Brazil, subsidized by the Brazilian Government, and sponsored by the United States Government, through its Inter-American Affairs Institute and the medical departments of the United States Army and Navy.

SAN FRANCISCO

Several San Francisco Bay Region doctors have been appointed **civilian consultants to the Secretary of War.** They will aid the Army in maintaining the highest standards of medical practice, according to Major General Norman T. Kirk, the Army Surgeon General. The appointments included: Dr. John J. Sampson, Dr. William J. Kerr, Dr. Edward Campion, Dr. Karl W. Bowman, Dr. Alexander Simon, Dr. Charles D. Aring, Dr. Carleton Mathewson, Dr. Leonard B. Bernard, Dr. Frank W. Lusignan, Dr. Thomas E. Gibson, Dr. William A. Sumner, Dr. Eugene S. Hopp, Dr. Walter P. Work, Dr. Paul C. Samson, Dr. Frederick C. Cordes, Dr. Max Fine.

Suggestion that planes be processed to prevent transfer of fleas, rats and other disease carriers in overseas air travel was made by **Dr. J. C. Geiger,** San Francisco public health director, before a recent meeting of the Pacific Association of Railway Surgeons. At the same time, he said, passengers should be examined for quarantine. A system for international controls, he added, was already being formu-

lated and international health bureaus could be in operation within two years.

Announcement of the appointment of **Dr. John Welch Brown** to the Professorship of Preventive Medicine and as Director of Student Health at the University of Wisconsin was made by Dr. Wm. S. Middleton, Dean of Medicine at that institution. Dr. Brown, whose appointment became effective November 1, 1946, received his M.D. degree from the **University of California** in 1935. He has served as Director of Clinical Laboratories, University of California Hospital, and as Assistant Professor of Medicine, University of California Medical School. He was on war leave from November, 1941, to December, 1945.

SAN JOAQUIN

Dr. Arthur Sonnenberg, who was formerly located at 48 East Ninth Street, Tracy, has moved to his new medical building at 49 East Tenth Street.

SANTA CLARA

Dr. Donald George Marquis, Stanford graduate of 1928 and assistant in neuro-anatomy at Stanford Medical School in 1929-30, was elected president of the American Psychological Association at the annual meeting of the organization in Philadelphia in September. Dr. Marquis, who was a fellow in medicine at Stanford in 1928-30, continued his studies at Yale University, where he subsequently held various posts in the department of psychology, becoming head of the school in 1941. Last year he went to the University of Michigan, where he is now chairman of the psychology department.

SONOMA

Dr. A. Morse Bowles, Santa Rosa physician and surgeon, who earlier this year was elected secretary of the general surgery section of the California Medical Association, has been elected ex-officio member of the scientific assembly to map the program for the 1947 convention of the Association to be held April 30 to May 3 at the Biltmore Hotel in Los Angeles. Included in the assembly are: Dr. L. Henry Garland, chairman, Dr. J. Homer Woolsey, Dr. Howard F. West, Dr. Clayton D. Mote, Dr. Howard O. Dennis and Dr. Bowles.

YOLO

Dr. R. D. Brundage, formerly of Nebraska, has taken over the practice of **Dr. W. D. Garcelon** in Esparto. Dr. Garcelon has moved to Sacramento.

At a recent meeting, Yolo County supervisors voted three to two against a proposal to open the new **Yolo General Hospital** to pay patients. Private physicians who attended the meeting sought the opening of the hospital immediately.

GENERAL NEWS

Doctors of medicine are needed for appointments on a full-time basis in the Las Vegas and San Bernardino offices of the Veterans' Administration to conduct physical examinations and render out-patient treatment.

A letter from the San Bernardino office of the Veterans' Administration describes the appointments:

"The doctor would be hired on a 40-hour week basis and the **salary range** would be determined by our Professional Standards Committee at Branch 12 in San Francisco. We desire very much and will make every effort to have the doctors appointed in the Department of Medicine and Surgery, Veterans' Administration, at the full grade for which the salary range is $5,905.20 to $6,802.00 per annum. However, if this is not approved by Branch 12, the appointment would likely be at the associate grade with the salary range of $4,902.00 to $5,905.20 per annum, in which case, the doctors would become eligible for promotion to full grade after six months of thoroughly satisfactory service."

The scientific exhibit at the Centennial Session of the **American Medical Association** to be held in Atlantic City, June 9 to 13, 1947, will include both the history of medicine during the past century and the latest developments of medical science.

Application blanks for space are now available. All applicants must fill out the regular form. Applications close January 13, 1947, after which the Committee on Scientific Exhibit will make its decision and notify the applicants.

Application blanks should be procured as soon as possible. They are available from The Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago, 10, Illinois.

The National Gastroenterological Association announces its annual **cash prize award contest** for 1947. One hundred dollars and a certificate of merit will be given for the best unpublished contribution on Gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. **The award is to be made** to the winner at the annual convention banquet of the Association in June of 1947. The Association reserves the exclusive right of publishing the winning contribution, and those receiving certificates of merit, in its Official Publication, "The Review of Gastroenterology." All entries for the 1947 prize should be limited to 5,000 words, be typewritten in English, prepared in manuscript form, submitted in five copies, accompanied by an entry letter, and must be received not later than April 1, 1947. They should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23, New York.

Two Californians have been appointed to the staff of the Associated Medical Care Plans, a national coordinating agency sponsored by the American Medical Association with Chicago headquarters. Frank E. Smith, Los Angeles, professional relations director for C.P.S. in Southern California, has been appointed director of the AMCP and William M. Bowman, executive director of C.P.S., will serve as vice-president of a twelve-man commission for the organization.

The appointments were made at the first annual meeting of the AMCP in Chicago last month.

Mr. Smith, with C.P.S. for two years, will establish residence in the headquarters city and Mr. Bowman will continue in his present capacity here.

A clearing house for more than 40 physicians' service organizations in 31 states, the AMCP has as its major objective the assurance of reciprocity among the services in these states and the eventual standardization of benefits.

INFORMATION

Purpose and Progress of the Hospital Survey in California

P. K. GILMAN, M.D.,* *San Francisco*

To attain the proper integration and extension of hospital services to meet the public need requires the complete support and cooperation of all groups in a body politic. That a beginning has been made is evidenced by an increasing realization that the hospital is a responsibility of the community and not of the individual. This communal interest demands equal participation and cooperation from those administering the institution, the physicians working in it, and the general public whose members will make use of the facility. The closer such cooperation is the better will the hospital fulfill its functions in the area as the distributing center for all types of medical service—preventive, diagnostic, therapeutic—and for the continuing education of doctors, dentists, nurses and the related professions.

The Commission on Hospital Care is a non-government public service committee, inaugurated by the American Hospital Association prior to the introduction of legislation in the Congress concerned with hospital construction, and is to study hospital service in the United States. This commission planned the state surveys and inventories of hospital facilities and is assisting state study groups by providing technical consultants and by tabulating data from questionnaires.

The public is becoming more hospital-minded and realizes that such institutions are a necessity. In our California hospitals the standards of service are high and, compared to other countries, we have more beds per population unit. However, the distribution of these facilities is by no means equal, many areas being under-supplied or with none.

How may these inequalities best be done away with? Surely not by uncoordinated and local planning controlled by local prejudices.

Broad planning on a state-wide basis is essential if facilities are to be made available to the people in all sections, and a necessary preliminary to such intelligent planning is a complete and detailed survey of existing institutions.

LEGISLATURE PROVIDES FOR SURVEY

Such a survey in California is being carried out by the State Department of Public Health and was made possible by legislation enacted at the 1946 special session of the legislature. This act provides for the making of a survey of the hospital and health center facilities and needs of the state and the developement of a program for the construction of hospitals and health centers. There is also created a State Advisory Council on Hospital Facilities to consult with and advise the State Department of Public Health in carrying out the purposes of the act. Further, the State Department of Public Health is designated the sole agency to make application on behalf of this state for any federal funds, to accept such funds and provide for their expenditure to assist in future construction.

The Association of California Hospitals, through its officers and members, has cooperated whole-heartedly with the Bureau of Hospital Surveys in the task of conducting a study of the 566 institutions giving active in-bed care in California, excluding federal and custodial facilities.

To date, 420 questionnaires have been returned. These will be sent to the office of the Commission on Hospital Care in Chicago and the data transferred to duplicate sets of punch cards. One set will be retained at headquarters to form part of the nation-wide picture, the other will be returned to the office of the State Department of Public Health where utilization of the information will enable the Bureau to estimate the adequacy of present facilities in the various parts of the state and then to evolve recommendations as to where and what types of institutions are necessary to make such facilities available to all the people. Such planning and resulting recommendations must, as stated above, be done and made on a state-wide basis and include recommendations for the extension of and addition to certain already existing facilities, as well as new construction in areas devoid of such conveniences.

STUDY TO AVOID COSTLY ERRORS

Before making definite recommendations as to site, size and type of facility, each community must be carefully studied if costly errors are to be avoided. Many factors will have to be considered thoroughly, such as population and population trends; relation to urban areas; income level and standards of living; distance, as influenced by topography, roads and means of transportation. These are among the many factors which decide the area to be served, the number of beds and the support that will be accorded the completed facility.

Today it is especially important that careful planning precede the erection of added facilities, as the cost of hospital service and construction has more than trebled during the past few years. Unless there is close cooperation between an economical hospital administration, a wholehearted community and professional support, the cost of maintaining a hospital may prove prohibitive for those seeking care.

There are today two channels through which financing of non-profit hospital facilities may be augmented.

In California, Senate Bill 586 relates to the establishment, organization, government and powers of hospital districts. Under this act a petition signed by registered voters of the proposed district is the first step. The necessary signatures must equal in number at least 15 per cent of the number of votes cast in the proposed district for the office of governor at the last preceding election at which a governor was elected. Such petition is presented to the supervising authorities of the county, precincts are established and if a majority of the vote is favorable, within each county's supervisorial district, the supervising authority shall declare the district duly organized. Such districts may include incorporated or unincorporated territories or both, but may not include part of a county having a population in excess of 200,000. The number of written protests required to terminate the proceedings shall be a majority of the registered voters residing in the proposed district.

A hospital district is administered by a board of directors and may raise funds in one of three ways: annual

* Chief, Bureau of Hospital Surveys, Division of Preventive Medical Services, California State Department of Public Health.

assessment up to 20 cents for each hundred dollars of the assessed value of all taxable property within the district, special assessment if two-thirds of the voters of the district approve, or by bonds also calling for similar approval by the voters of the district.

The second means of aiding construction is by federal funds. The Hill-Burton Bill was recently enacted into law and proposes federal assistance to the states. The bill, as passed, appropriates funds on a matching basis (33 1/3 per cent federal funds to 66 2/3 per cent local) for the purpose of assisting the states in carrying out the survey of present facilities, determining the need for construction and developing a program for construction of such public and other nonprofit institutions as will furnish adequate hospital, clinic and similar service to all the people. Three million dollars was appropriated for this purpose.

In addition the act authorizes appropriation of $75,000,000 annually for a period of five years for the construction of public and other non-profit hospitals. If and when such monies become available California will stand to receive approximately $1,900,000 a year for the five-year period. This likewise will be available for 33 1/3 per cent of approved projects presenting reasonable assurance that adequate financial support will be available for their construction as well as maintenance and operation when completed.

Four walls and beds are but one factor in supplying hospital needs in a community. The quality of service offered the public and the availability of physicians determine the standards of the institution. While proper facilities go a long way toward attracting physicians, adequate income must be assured as well as opportunities for further study and the availability of advantages often lacking in isolated areas.

As a result of this survey, it is hoped a program will be evolved that will plan a system of hospitals and health centers each supplementing the others rather than competing. That this must ensue is obvious if proper standards are to be maintained and the type of service made available that will justify the existence of the institution.

Surplus Equipment Orders Exceed Supplies

California medical veterans awaiting or planning purchase of medical equipment from war surplus stocks are cautioned by the Los Angeles and San Francisco regional offices of the War Assets Administration that demand for popular, major items far exceeds supply.

Medical equipment set aside for sale to medical veterans has been apportioned regionally on the basis of veteran population of the 33 WAA regions in the United States, but quantities so far allocated are comparatively small and well below orders already on hand.

To permit a nation-wide inventory and a count of veterans by WAA regions, sales of medical equipment and supplies were "frozen" last June 10. The "freeze" was lifted August 23, and the new apportionment formula was placed in effect. Distribution is now in progress, with priority holders being notified as rapidly as items on their priority lists are allotted to the two California regional offices.

Under the new formula, the Los Angeles WAA office receives 4 per cent and the San Francisco offices 3 per cent of WAA stocks of medical equipment. A comparison of orders on hand, for which priorities have been issued, with the total of allocations for the two California regional offices under the new plan indicates the unbalanced demand-supply situation. For seven popular, major items of medical equipment those figures are:

	Los Angeles		San Francisco	
Item	Orders	Allotments to Sept. 23	Orders	Allotments to Sept. 23
Diathermy apparatus	192	0	35	0
Basal metabolism machines	112	3	37	0
Electrocardiographs	136	0	28	0
Medical x-ray machines	265	38	50	18
Examining tables	162	21	75	2
Operating tables	83	25	35	94
Microscopes	249	4	204	0

The new apportionment policy corrects a confused and unbalanced condition created by handling of war surplus by seven federal agencies, before surplus sales were centralized in WAA on March 25, 1946. It also distributes to all WAA Regions, medical equipment formerly available only in those regions where warehouses of the medical sections of the services were located. As there were no such warehouses in California, very few major items were available in this state until the new plan went into effect.

In spite of the demand-vs.-supply situation of major items, WAA invites medical veterans who have not obtained their priority certificates to file applications at their earliest convenience. Some items, particularly of supplies (as distinguished from equipment) will be in such quantity that most priority holders will be able to fill their needs. Such orders are filled in the numerical order of priority certificates, which means that the earlier the certificates are obtained the sooner the order is filled

REFRESHER COURSE ON DIAGNOSIS OF NEOPLASTIC DISEASE

The California Cancer Commission, with the support of the California Division of the American Cancer Society, will present early next year a refresher course for the general physician under the supervision of the Tumor Board of the Los Angeles County General Hospital.

The course will be held from January 6-8, 1947, inclusively, with day and evening clinics. Hotel reservations are anticipated for members and wives who may desire to attend. Accommodations are planned for one hundred physicians.

The program is aimed to cover all the usual types and locations of cancer and allied diseases with special emphasis on information and procedure pertaining to diagnosis. The presentation will include tumor pathology, patient demonstrations whenever possible, and illustrated didactic lectures in all the specialties. Instructors are selected from the faculties of the Univeristy of Southern California Medical School and the College of Medical Evangelists according to their specialties in the connection with the Tumor Board of the Los Angeles County Hospital.

The California Division of the American Cancer Society, in sponsoring this program, has made the course available to any physician in Southern California without charge.

Since facilities limit the accommodations, reservations are now being accepted, and the Cancer Commission asks that interested physicians send their applications at once

to Edward M. Butt, M.D., 1930 Wilshire Boulevard, Los Angeles 5, California.

Schedule of the three-day refresher course follows:

MONDAY, JANUARY 6, 1947

9:00 a.m.—Welcome by the Cancer Commission—Dr L. C. Kinney, Chairman.

9:15 a.m.—The Opening of the Refresher Course—Dr. B. O. Raulston.

9:30 a.m.—General Tumor Pathology—Dr. Ernest M. Hall.

9:50 a.m.—Historical Development, The Cancer Problem—Dr. Ian Macdonald.

10:30 a.m.—Experimental Cancer Research — Dr. H. Pearson.

11:00 a.m.—Biochemistry of Growth—Dr. Duel.

11:30 a.m.—Theories on the Nature of Cancer—Dr. Edward M. Butt.

12:00 noon—Luncheon.

Dr. H. P. Jacobson, Chairman

1:00 p.m.—The Biopsy—Dr. John Budd.

1:30 p.m.—New Patient Clinic—Dr. Leo M. Levi, Dr. Ian Macdonald.

3:00 p.m.—Tumors of the Skin—Dr. Maximilian E. Obermeyer.

5:00 p.m.—Pathology—Dr. Nelson P. Anderson.

Surgery—Dr. William S. Kiskadden.

Radiation—Dr. Horwitz.

7:00 p.m.—Dinner.

8:00 p.m.—Joint Meeting with Surgery Section of the Los Angeles County General Hospital—Dr. C. J. Berne, Chairman.

Tumors of Thyroid—Dr. Isaac Y. Olch.

Tumors of Stomach—Dr. E. J. Joergensen.

Tumors of Colon—Dr. Phillip Cunnane.

Tumors of Rectum—Dr. William H. Daniel.

Roentgenographic Summary — Dr. Wilbur Bailey.

TUESDAY, JANUARY 7, 1947

Dr. Leroy Sherry, Chairman.

9:00 a.m.—Surgical Pathology—Dr. L. J. Tragerman.

10:00 a.m.—Tumor Surgical Clinic—Dr. C. J. Berne.

12:00 noon—Luncheon.

1:00 p.m.—Oral, Pharyngeal, Laryngeal Tumors—Dr. J. McKensie Brown, Chairman.

Larynx—Dr. Simon Jesberg.

Pharynx—Dr. Stewart Harrison.

Oral—Dr. George Sharp.

3:00 p.m.—Chest Tumors—Dr. John Jones.

4:00 p.m.—Brain and Cord Tumors—Dr. Cyril B. Courville, Dr. Rupert B. Raney.

7:00 p.m.—Dinner.

8:00 p.m.—Genito-Urinary Tumors — Dr. Alvin G. Foord, Chairman.

Tumors of Bladder—Dr. J. J. Crane.

Tumors of Prostrate—Dr. H. C. Bumpus, Jr.

Tumors of Kidney—Dr. Donald A. Charnock.

9:00 p.m.—Bone Tumors—Dr. Paul McMasters.

Benign Tumors—Dr. Keasby.

WEDNESDAY, JANUARY 8, 1947

9:00 a.m.—Tumor Board—Dr. H. P. Jacobson, Chairman.

11:00 a.m.—The General Physician's Obligation to Neoplastic Disease—Dr. Wilbur Bailey.

The Legal Responsibility of the General Practitioner to Neoplastic Disease — Dr. Louis J. Reagan.

12:00 noon—Luncheon.

1:00 p.m.—Gynecological Clinic—Dr. William E. Costolow, Chairman.

Pathology—Dr. Curtis.

Cancer of Cervix—Dr. Leo M. Levi.

Cancer of Fundus—Dr. Henry N. Shaw.

Tumors of Ovaries—Dr. Herman S. Hendrickson.

3:00 p.m.—Leukemia—Dr. G. Carpenter.

Hodgkin's Disease—Dr. George Sharp.

7:00 p.m.—Dinner.

8:00 p.m.—Breast Seminar—Dr. Lawrence Chaffin, Chairman.

Pathology—Dr. Hugh A. Edmondson.

Method of Biopsy—Dr. Alvin G. Foord.

Benign Tumors—Dr. Ian Macdonald.

Cancer

The Radical Mastectomy—Dr. C. J. Berne.

INDUSTRIAL INJURY REPORTS MANDATORY

The California Labor Code in Section 6407 requires every physician or surgeon who attends an injured employee to file with the Division of Labor Statistics and Research of the California Department of Industrial Relations a complete report of injury. These reports are prepared on Form 21, "Physician's or Surgeon's Report of Injury" furnished by the Department.

The Division of Labor Statistics and Research is formulating a program to compile current and detailed statistics of industrial injuries for California for accident prevention purposes and all physicians and surgeons are urged by the Department to file *promptly* the reports required by law. Punctual filing of the reports will expedite payment of compensation benefits to injured workers and also payment of the doctor's fee, the Department says.

The Physician's or Surgeon's Report of Injury should be sent to the Division of Labor Statistics and Research, 507 Polk Street, San Francisco 2. Forms can be secured by writing to that address.

Letters to the Editor . . .

POST-ONCOLYTIC IMMUNITY

During studies on the extraction of substances from induced primary and transplanted rat sarcomata, Aptekman[1] and his associates of the Wistar Institute of Anatomy and Biology, and the Carnegie Institute, Washington, D. C., obtained an alcohol-soluble fraction that inhibited growth of tumor grafts and conferred immunity from further growth of homologous grafts in a large percentage of the treated rats.

All experiments were done on pure inbred strains of white rats. Sarcomas were produced in these rats by the injection of a carcinogenic agent into the right axilla. After the sarcomas had grown to a large size (50 x 25 x 20 mm.) a small amount of the tissue was used for transplantation into other rats of the same strain. The remaining tissue was finely ground, mixed with an equal volume of 95 per cent alcohol, and allowed to stand for 24 hours at refrigerator temperature. The mixture was then filtered and two volumes of 95 per cent alcohol added to the filtrate. After a second refrigeration the resulting precipiate was filtered off. The clear filtrate thus obtained was concentrated to about one-tenth of its original volume by vacuum distillation. The final product was a somewhat cloudy "concentrate" with an alcohol content of from 15 to 26 per cent.

Rats of one litter were implanted on the right side with approximately equal sized grafts of tumors native to their strain. When the grafts had attained a size of about 20 x 8 x 5 mm., part of the rats were injected intratumorally daily with 0.5 to 1 cc. of homologous concentrate. Other rats were left untreated to serve as controls, or were injected with a control solution. Among these controls were: extracts from beef muscle, from normal rat tissue and solutions containing known amounts of alcohol.

Fifty-six of the 58 tumors thus treated were destroyed from three to five and occasionally as many as nine to fourteen injections being required for complete oncolysis. No oncolysis was noted in 45 litter-mates similarly injected with control solutions. Some of the tumors treated with control solutions became necrotic and opened to the surface. Nevertheless, the malignant cells continued to multiply and the tumor increased in size until it brought about the death of the host. Not one of the 25 rats healed by the "concentrate" and kept alive for many months had a recurrence of the tumor.

The remaining 32 healed rats were implanted on the opposite side with a graft of the same type of tumor as that destroyed. The grafts grew in every one of the untreated control rats, but failed to grow in 25 (78.1 per cent) of the 32 rats whose tumors had been destroyed by injections of "concentrate." These 25 apparently immune rats were later implanted with graft of a second sarcoma that had originated in the same strain. Fifteen of these rats proved to be resistant to growth of these heterologous grafts.

Five healed and immune female rats were mated with five healed and immune males. When the offsprings were 30 days old, they and their parents were engrafted with a fragment of the same kind of tumor which had undergone oncolysis in the parent. The grafts grew in every one of the offspring, but did not grow in the parents.

This work is of basic theoretical interest since it is the first experiment in which the injection into tumors of an oncolytic substance has brought about an immunity to tumors homologous to a specific rat strain. Heterologous post-oncolytic tumor immunity was previously reported by Gross,[2] Lewis[3] and others. Attempts to determine the exact mechanism of this post-oncolytic homologous tumor immunity are now in progress.

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"CANCER OR CANCERS?"

Cancer or cancers? Oberling,[5] in his excellent monograph, "The Riddle of Cancer," answers this question in a manner generally satisfactory to students of the subject:

> "To the experimentalist the idea that cancer is a whole group of disorders, each with a different cause, is wholly unsatisfactory since no matter how strongly the etiological dissimilarities be emphasized cancer to him is one disease, and one disease only. He sees always the same cellular derangement, marked by exalted proliferation, invasive growth, and above all the impudent independence that is called autonomy."

Although the tissue in which the cancer cell primarily arises contributes, through local tissue reactivity, a superficial histological definitiveness to the malignant lesion so that gastric carcinoma is, for example, usually distinguishable from carcinoma of the esophagus, the identity of the site of origin becomes less certain as the malignancy of the tumor increases. In other words, as the number of definitive cancer cells within a tumor increases, the lesion bears a decreasing resemblance to the tissue within which it arose so that the most malignant tumors, generally, resemble the tissue of their origin least and each other most.

Modern pathology has generally discarded any but a tentative morphological distinction between carcinoma and sarcoma.[2] Any attempt to sustain rigid distinctions in the classification of the infinite gradations in the exhibition of the notably pleomorphic cancer cell must lead to complete failure. Past efforts in the classification of cancer are reflected in such terms as "carcinosarcoma," "sarcocarcinoma," "sarcomatoides," "pseudo-carcinoma," etc. Even such expansive nomenclature proves inadequate to describe the not uncommon instances in which a carcinomatous exhibition of cancer is found merging into or metastasizing as sarcoma, or vise versa. Although most exhibitions of cancer in man appear undoubtedly to reflect a common fundamental process, the classification of cancers according to their anatomical site and degree of anaplasticity, of course, remains clinically a practical necessity.

In examining the so-called "etiological dissimilarities" in cancer, a distinction should be made between contributory etiological factors and the final-common-pathway by which the effects of these diverse factors are mediated. Thus we may speak of many etiological agents for inflammation, and yet recognize a chain of morphogenetic phenomena common to them all. If it is true, therefore, that all cancers represent essentially the same morphogenetic process, it follows that careful examination of the nature and etiology of a specific exhibition of cancer

should afford clues as to the property of all malignant tumors.

In a summary which he wrote in 1903, Marchand first pointed out that chorionepithelioma possesses great theoretical importance in regard to tumor formation. At that time the polemic on the maternal vs. the foetal origin of chorionepithelioma had not yet been resolved, though the weight of evidence was already tipping in the direction of Marchand's thesis of 'foetal" origin.

That primary uterine chorionepithelioma represents the cancerization of the maternal host by the trophoblast of the conceptus is now universally accepted. And though the malignancy of this tumor is not exceeded by that of any known exhibition of cancer, it is significant that the so-called malignant cell here is a trophoblast cell (Langhans cell) indistinguishable morphologically or biologically from the same cell in the chorion of normal pregnancy.[6] In other words, primary uterine chorionepithelioma represents the simple overgrowth of the physiologically malignant trophoblast[1] as a result of the lack of a humorally mediated substance by which such overgrowth is prevented in the course of normal gestation. This is shown by the fact that when the trophoblast plus the definitive ambryo are cultured *in vitro* the trophoblast erodes, infiltrates and destroys the latter in, as Maximov phrases it, "the absence of the checking influence of the mother."[4] Thus it is clear that one of the most malignant exhibitions of cancer known may arise without the mediation of "mutations," viruses or chemical carcinogens.

The morphogenesis of primary uterine chorionepithelioma and its metastases is clear. Following the meiosis (gametogenesis) of a diploid totipotent cell, a haploid gasetogenous cell is produced which, in the normal process of reproduction, is activated by fertilization. Following this the trophoblast is segregated from the non-trophoblast cells of the early conceptus: and it is the trophoblast that, through its "physiologically malignant" properties, infiltrates the maternal host to establish an adequate decidua. Failure of the host to check this trophoblastic growth, of course, may result in the overgrowth of chorionepithelioma. It is not, therefore, without significance that such chorionepithelioma represents the only exhibition of cancer in which an introduction of a new cell type does not accompany the so-called malignant change.

It is significant, however, that chorionepithelioma is not always confined to the reproductive organs nor is it found only in the female. Testicular chorionepithelioma as well as primary extra-genital chorionepitheliomas in both sexes present cytotrophoblast that is indistinguishable from that of the normal pregnancy trophoblast. It is generally accepted that testicular chorionepithelioma arise from germ-cells (diploid totipotent cells[2]), but the fact is usually overlooked that such cells must first undergo meiosis to produce the trophoblast-competent gametogenous cell that has, as the only alternative to death, the initiation (by division) of a genetically unique life-cycle through the initial production of trophoblast. It is thus of the utmost theoretical importance that the trophoblast cell has *never* been found outside the canalization of normal pregnancy except as one of the most malignant exhibitions of cancer. And unlike all other cells of the life-cycle, the trophoblast cell is the only cell that has never been found ectopically except as cancer.

In recent years several well authenticated cases of primary extra-genital chorionepithelioma in the male have been reported. Of these a case described by Stowell Sachs and Russell[7] of a primary chorionepithelioma of the pineal gland of a 15-year-old boy is of particular interest, since scrupulous serial examination of the testes apparently ruled out the possibility of an obscured primary testicular growth. The low level of tissue reactivity in the pineal gland and brain probably accounts for the fact that the trophoblast cells were not obscured nor masked as they so frequently are in testicular growths, for example, where the bulk of them may be exhibited in the matrix of somatic tissue of adenocarcinoma, seminoma or sarcoma and where only small nests of overt chorionepitheliomatous cells, plus the cytotrophoblastic prolan in the urine, attest the trophoblastic nature of the malignant component.

A number of primary genital as well as extra-genital chorionepitheliomas have been reported in which the overt trophoblast cells have merged by imperceptible degrees into the "masked" trophoblast of adenocarcinoma or sarcoma—or metastasized as such. And primary sarcoma and adenocarcinoma have been described as metastasizing as chorineonepithelioma. It is clear, therefore, that if we accept the thesis of the fundamental identity of all exhibitions of cancer and understand the morphogenetic phenomena of but one type—chorionepithelioma—it follows that we must ascribe the same phenomena to the remaining types. Besides being Euclidean in its clarity this deduction is consonant with the axiom that cells of the same type arise from preexisting cells of the same type, as expressed in Bard's extension of Virchow's famous dictum of *omnis cellule e cellule* to *omnis cellula e cellula ejusdem generis.* While the trophoblastic nature and diploid-totipotent-cell origin of all exhibitions of cancer is the certain corollary of the concept of the fundamental identity of them all, any alternative to the unitarian thesis, in view of the evidence yielded by chorionepithelioma, will inevitably lead to a *reductio ad absurdum.*

Morphogenetically, then, the common malignant component in all exhibitions of cancer is the trophoblast cell (however masked morphologically) and the common cell of origin is the ubiquitous totipotent cell, the potency of which has been reserved since early cleavage. This simply means that the cancer cell is the most primitive cell in the life-cycle of the animal: that this cell is normally a component of the life-cycle and does not arise through spontaneous generation. This, of course, is consistent with the imperfectly defined and widely held idea of the "embryonic" nature of cancer.[3] And just as the presence of bacteria or other foreign agents in the body can evoke a wide variation in the kinds of tissue reactivity, depending upon the tissue affected, etc., so can the ectopic trophoblast cell elicit a variety of exhibitions of cancer besides frank chorionepithelioma.

The means by which such etiological agents as the chemical carcinogens, certain metabolites, possible viruses, radiation, etc., converge into the final-commonpathway mediating the meiosis of the totipotent cell and the activation of the consequent gametogenous cell to trophogenesis are not fully understood. To say that such action is one of organizer stimuli upon competent cells is merely to restate rather than to explain the phenomenon.

Certainly, further advances in our knowledge of the endocrinology of reproduction promise to answer many questions in the field of oncology; while the means by which the conceptual trophoblast is first checked in its growth and then destroyed in the course of normal gestation, probably offers a very rewarding route for further investigation.

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BOOK REVIEWS

PRACTICAL MALARIOLOGY. By Paul F. Russell, M.D., M.P.H., Colonel M.D., A.U.S., Parasitology Division, The Army Medical School, Luther S. West, Ph.D., Head of Biology Department, Northern Michigan College of Education. Major, Sn.C., A.U.S. (Reserve); formerly Entomologist, Parasitology Division, Army Medical School, and Reginald D. Manwell, Sc.D., Professor of Zoology, Syracuse University, New York, formerly Captain, Sn.C., A.U.S., Protozoology Section, Parasitology Division, Army Medical School. Forward by Raymond B. Fosdick, President of The Rockefeller Foundation. 238 illustrations, 8 in color. W. B. Saunders Company, Philadelphia, 1946. Price $8.00.

Many American physicians had experience with malaria for the first time in World War II. Knowledge concerning this most frequent of diseases was greatly advanced by the war. Suppressive chemical therapy, and particularly control of malaria by the use of measures such as D.D.T., greatly altered the military story of the Pacific Theater.

This excellent book outlines the whole problem of malariology and includes much material available through the National Research Council. Readers who served in the military forces will find in it much to refresh their memories of experiences in the tropics.

It should be emphasized that the study of malaria is not just a clinical study, but one encompassing all aspects of the disease. In fact in this book only 60 of the 661 pages deal with the disease in man. The remainder are divided into sections on the parasite, the mosquito, the community, prophylaxis and control and into an appendix with a key to world anophelines.

As stated in the title the book is practical. It is a beautiful piece of work, well illustrated, attractive and clear. All students of the subject will find pleasure in reading this volume, and those in the field will find it concise, practical and useful.

THROUGH THE STRATOSPHERE—THE HUMAN FACTOR IN AVIATION. By Maxine Davis. Cloth. Price, $2.75. Pp. 253. New York: The MacMillan Company, 1946.

The glamor which surrounds aviation is made of resilient material. This time it encloses the story of aviation medicine. Miss Davis is a reporter, an observant one. She has obtained her information from headquarters and from flying fields. In a very clear introduction she outlines her tale as that of a journalist, and throughout the book she records in most interesting fashion her personal experiences, mixed with official material from the Pentagon. If she has been too credulous in the acceptance at face value of some of the latter she has erred very humanly. The interpretations of technical programs are well done, even though they may at times be difficult for the layman. The descriptions of men and of places will recall pleasantly one's own experiences if one has been with the air forces.

The details of the story begin with a description of the fliers' classification program of the U. S. Army Air Forces. Next is an account of the hazards of altitude—cold and anoxia. Various other aspects of aviation medicine are covered in order: G-suits, the care of fliers and their equipment, food, the prevention of infectious disease, actual personal medical care, visual aids, parachute descent, combat fatigue and flying fatigue, air evacuation and convalescent care. The specific roles of the squadron flight surgeon, the personal equipment officer, the flight nurse and the air-ground rescue unit of the C.B.I. Theatre are developed.

In summary, one may term this a layman's textbook of aviation medicine in World War II. It is recommended reading.

THE NORMAL ENCEPHALOGRAM. By Leo M. Davidoff, M.D., and Cornelius G. Dyke, M.D. Second Edition, Thoroughly Revised, Illustrated with 155 Engravings. Lea & Febiger, Philadelphia. Price $5.50.

Dr. Davidoff and Dr. Dyke (now deceased) have both had extensive experience in the study and interpretation of Encephalograms as well as with the associated surgical problems.

This volume presents a complete story of the historical development of Encephalography and the various technical methods employed in the introduction of gases into the subarachnoid spaces and the ventricular system.

The roentgenological aspect is also covered, both as technique and interpretation of the films.

The indications and contraindications, as well as the reactions to encephalography, are discussed in detail.

Considerable space is devoted to the appearance of normal encephalograms and a careful analysis is made of the entire ventricular and subarachnoid systems as they appear in the films. This section is well illustrated with numerous roentgen ray films in addition to diagramatic illustrations and photographs of anatomical specimens.

This monograph is comprehensive in every detail and should be a part of the library of all Neurologists and Neurosurgeons, as well as Roentgenologists who are interpreting encephalograms.

ESSENTIALS OF MEDICINE. By Charles Phillips Emerson, Jr., A.B., M.D., and Jane Elizabeth Taylor, R.N., B.S., M.Ed. Fifteenth Edition. 201 Illustrations in Black and White and Four Color Plates. Copyright, 1946, by J. B. Lippincott Company, Philadelphia. Price $3.50.

This book, now it its 15th edition, ranks among the best of its kind. The new edition has been carefully revised, brought amazingly up to date, and seems destined for wide acceptance by those engaged in the instruction of nurses.

Noteworthy, it seems, is the masterly balance maintained between the wealth of facts contained, and their practical application in nursing. Somewhat difficult medical subjects are rendered more easily understandable by the physiologic approach, with nursing techniques often being emphasized as a part of this physiologic concept. The book is well illustrated, and the new double column type will no doubt be appreciated by students. The new unit arrangement for consideration of subject matter (one unit being devoted particularly to nursing care) certainly seems an improvement over former editions. Quite naturally, one could find ground for slight disagreement with the medical author on certain statements in the text, but these disagreements are of no moment, and would serve only to detract from an excellent work.

The book is recommended to those who are seeking a text for teaching nurses the fundamentals of internal medicine.

DIAGNOSIS AND TREATMENT OF ACUTE MEDICAL DISORDERS. By Francis D. Murphy, M.D., F.A.C.P. Second Edition, 27 Illustrations, 510 Pages. F. A. Davis Company, Publishers, Philadelphia. 1946. Price $6.50.

This medium sized volume is devoted to the practical considerations in the management of the acute episodes of medical diseases. It is the accumulation of a lifetime of the author's experiences. The print is large and clear. Scattered sparsely through the work are illustra-

tions covering special points. This volume is the second edition. The first edition was published in 1945.

The contents are divided into 25 chapters such as Vascular Disease, Diseases of the Blood, Heart, Metabolism, etc. The author no doubt had good reasons for dividing the heart into four chapters, the lungs into three chapters, etc. It is felt that it would clarify the matter, however, if topics relating to one subject, such as the heart, be grouped under one chapter. Sub-topics might be arranged to better advantage in their respective chapters, e.g. Tetany with Hypoparathyroidism instead of with the section on Diabetic Coma; Subarachnoid Hemorrhage grouped with Cerebral Hemorrhage instead of following the topic Carotid Sinus Syndrome; Lung Abscess with the Pneumonias, etc. The above suggestions seem to group related topics closer together.

Since new editions are to come out, the author will keep the volume corrected to suitable new data in diagnosis and treatment. A few suggestions might be pertinent now: (1) Muscle Poisoning by the dinoflagellates, which is a serious acute medical emergency, seems more important in this country than the bite of a cobra; (2) BAL (dimercaptopronal) in the treatment of Acute Arsenic and Acute Mercurial Poisoning; (3) Propylthiouracil in the discussion on treatment of hyperthyroidism; (4) Penicillin may be a specific for psittacosis.

It is difficult for any one text to keep up with all of the advances in the clinical use of the sulfa drugs, Penicillin and Streptomycin. These drugs and antibiotics are best reviewed by reading current medical journals.

Aside from these minor points, the author is to be congratulated for his vision and for having written such an important book. It bridges the gap between a comprehensive text book and a small hand book on medical diseases. This volume should be an integral part of the library of the general practitioner and internist.

MEDICAL JURISPRUDENCE

MALPRACTICE; SUFFICIENCY OF EVIDENCE; CORRECTNESS OF DIAGNOSIS

HARTLEY F. PEART, ESQ., *San Francisco*

In a case sent to it on appeal, the District Court of Appeal rendered a decision in a malpractice suit arising out of the following facts and circumstances:

Plaintiff Mrs. R. consulted defendant, a physician and surgeon, relative to an itching in the region of her vagina. After taking plaintiff's history, defendant made a smear from the vagina, urethra and cervix, and, after a microscopic examination of the smear, told plaintiff that she had gonorrhea. Plaintiff and defendant then discussed the possible source of her infection, defendant telling her that in all probability she could have contracted the disease only by sexual contact. Plaintiff informed the defendant that the itching had occurred shortly after intercourse with her husband two days previously. Defendant then told plaintiff to talk to her husband or, if she preferred, that he would talk to him. Defendant prescribed treatment for the plaintiff which, among other things, consisted of tablets containing sulfanilamide.

Two days after defendant's consultation with the plaintiff, the plaintiff's husband consulted the defendant, who endeavored to obtain a smear from the entrance of the husband's urethra, but was unsuccessful. He did, however, obtain an imprint which he examined microscopically, and then expressed doubt to the husband as to whether he was afflicted with gonorrhea, but told him that he was convinced that his wife was suffering from the disease and he considered it advisable for the husband to commence treatment immediately. The husband never returned to the defendant for further treatment.

The next day the plaintiff and her husband went to another doctor who made smears and sent them to a laboratory for examination. The results of this examination were negative, whereupon this doctor declared that neither the plaintiff nor her husband was suffering from gonorrhea. A few months after this plaintiff and her husband commenced the present action against the defendant, whereupon the defendant sent the slide containing the smear from the plaintiff's wife, to two laboratories where the "gram negative stain" test was applied and both laboratories reported a positive reaction showing gonococci.

Plaintiff wife and her husband sought to recover damages from the defendant physician for alleged malpractice. The trial was had by the court without a jury and resulted in favor of the defendant physician. Plaintiffs appealed from that judgment. The District Court of Appeal of the State of California upheld the lower court and stated that there was insufficient evidence to sustain a judgment against the defendant in favor of either or both of the plaintiffs. In its discussion the court stated that it had to first answer the question of whether the evidence was sufficient to sustain a judgment against the defendant. The court held that in California a physician and surgeon is not required to make a perfect diagnosis, but is only required to have that degree of skill and learning ordinarily possessed by physicians of good standing practicing in the same locality and to use ordinary care and diligence in applying that learning in the treatment of his patients. Continuing, the court declared that the evidence in the instant case disclosed that it was the ordinary practice of physicians and surgeons in the community in making diagnoses for gonorrhea to use either the "methylene blue test" or the "gram negative stain test," saying further that at the time the plaintiff consulted the defendant he had made the methylene blue test which showed that she was suffering from gonorrhea. Subsequently, the same slides were submitted by him to two independent laboratories where the gram negative stain tests were made showing the presence of gonococci. The court concluded from this that there was substantial evidence to support the finding of the trial court that the defendant physician had used the requisite skill in diagnosing the plaintiffs' complaint. Further, that this was also true as to the defendant's conduct toward the plaintiff's husband.

The District Court of Appeal therefore affirmed the judgment of the lower court, which had held that the plaintiffs had failed to produce sufficient evidence to sustain a verdict against the defendant physician for alleged malpractice.